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# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Abstract

**Objective**: To study the impact of occupational silica exposure on the incidence rate of sarcoidosis and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries.

**Design**: The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses.

**Setting**: The personnel records from ten iron foundries were used to identify workers whose employment began before 2005 which was then linked to the National non-primary outpatient visits register.

**Participants**: The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. The cohort's employment period represents 23 807 person-years at risk.

**Main outcome:** The results presented in our study indicate that moderate to high levels of silica exposure increase the risk of sarcoidosis and seropositive rheumatoid arthritis.

**Results**: Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals.

**Conclusions** This study highlights the risk of silica exposure for both sarcoidosis and seropositive rheumatoid arthritis. We believe that the increased risk for both seropositive rheumatoid arthritis and sarcoidosis might be based upon the same cellular mechanisms.


## Strengths and limitations of this study

- This study identifies one possible trigger for Sarcoidosis as well as seropositive rheumatoid arthritis.
- This study draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis as the diagnosis is rather unusual.
- As this study is a register study we have no knowledge of other exposure that can trigger rheumatoid arthritis and Sarcoidosis.


## Keywords

Sarcoidosis, Rheumatoid arthritis, Silica

## Background

Sarcoidosis is an inflammatory disease that involves the formation of granulomas, mainly in the lungs and / or intrathoracic lymph nodes, but several other organs may also be affected (1). It is diagnosed by biopsy - usually via bronchoscopy if there is lung involvement. Sarcoidosis has no clear etiology, and it is estimated that it has an annual incidence of 11.5 per 100 000 in Sweden (2). Its frequency peaks among individuals aged between 20 and 45. Although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals (1, 3). One such suspected environmental factor is silica or silica dust, but only a few studies on silica and sarcoidosis have been published. An animal study showed that the silica administered via the gastrointestinal tract or intravenously promoted granuloma development in animals infected with mycobacteria (4). Additionally, there have been reports of persistent sarcoidosis going into regression upon cessation of silica exposure (5, 6). A cohort study of workers in a limestone quarry (diatomaceous earth) in Iceland yielded a sarcoidosis incidence rate of 9.3 / 100,000, compared to a value of 0.5-2.7 / 100 000 for the Icelandic population as a whole(7). While this was taken to suggest that silica exposure may increase the risk of sarcoidosis, the sample was so small that it would be difficult to draw firm conclusions(7). A large case-control study from the US suggested that silica is associated with a range of diseases in addition to silicosis, including lung cancer, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, and the autoimmune disease rheumatoid arthritis (RA) (8). While this study did find increased risks of various autoimmune diseases (including systemic lupus erythematosus (SLE) and systemic sclerosis) with silica exposure, it did not indicate any connection with sarcoidosis.

Silica exposure is known to cause a fibrotic and potentially fatal lung disease called silicosis (9). Silicosis is currently rare in Sweden because of legislation against silica and silica dust exposure, which has successfully reduced occupational exposure levels (10). This legislation also requires people who are occupationally exposed to silica dust to undergo regular medical checks including physical examinations with spirometry and chest X-rays to ensure the absence of lung disease (11). To study the impact of occupational silica exposure on the risk of sarcoidosis, we used a cohort of silica-exposed workers from Swedish foundries (10).

As silica exposure is also suggested to be important in other inflammatory diseases such as RA (8), we also investigated the risk of RA in the studied cohort. RA and sarcoidosis are both inflammatory diseases, albeit with different symptoms. As such, the environmental factors that trigger either disease in genetically predisposed individuals may be similar (1, 12).

Earlier studies have shown that seropositive RA can be initiated within the respiratory system by autoimmune responses to citrullinated peptides (13). A Swedish cohort study found that silica exposure combined with smoking is associated with an increased risk of developing anti-citrullinated protein antibody (ACPA) positive RA (12).

At our clinic, we have recently had some patients with pulmonary sarcoidosis who also experienced occupational exposure to silica. This prompted us to investigate whether silica dust could cause sarcoidosis, and since these patients now had sarcoidosis, whether it would be advisable for them to stop their occupational exposure to silica.

## Methods and statistical analysis

Data from ten iron foundries' lists of employees were available in this study (10, 14). The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded (Figure 1). The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment period represents 23 807 person-years at risk.

All Swedish residents have a unique personal identification number and equal access to health care and hospital services. This makes it possible to retrieve patient data from a variety of registers, creating unique opportunities to analyze morbidity across the entire patient population. Such nation-wide patient registers are well suited for epidemiological studies.

The cohort was linked to the "National non-primary outpatient care register", which is maintained by the Swedish National Board of Health and Welfare and contains data for all years since 2001. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).

The sarcoidosis morbidity analyses covered the period from 2001 (when the National non-primary outpatient care register started) through to 2013. Information on the workers' vital status and emigration status as of the 31$^{st}$ of December 2013 were obtained from the Swedish population registry.

The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then.

The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers.

The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.

A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures (mg/m$^3$) were used to calculate dose responses. Exposure to

respirable silica was thus defined as the average exposure per year in mg/m$^3$ and categorized into four dose groups (quartiles):<0.023 mg/m$^3$, 0.024-0.035 mg/m$^3$, 0.036-0.047 mg/m$^3$ and >0.048 mg/m$^3$. Because we lack data from before 1968, exposure times before this year were estimated based on the silica level after 1968. The exposures for the groups 'Other specified', 'Foundry workers' and 'Other unspecified' were taken to equal the mean exposure for all the other job classes. The exposure measurement database and exposure modelling are presented elsewhere (15).

## Patient involvement

No patients were involved in the design or conduct of this register study.

The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Results

Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years (Table 1). The total range for employment was 1 to 52 years and the mean length of employment was 11 years. As can be seen in Table 1, the cohort included workers representing a wide variety of job categories; the most frequent were fettler (20%) and core maker (11.3%). However, many of the workers had been employed in several different capacities during the study period (Table 1).

Silica exposure had been measured for all the job categories, and was found to vary between 0.0054-4.9 mg/m$^3$ (Table 2). The highest measurements were well above the Swedish occupational exposure limit (OEL) of 0.1 mg/m$^3$, but both the mean and median measurements for most job titles were below the OEL, with the exception of furnace and ladle repair (Table 2). Furnace and ladle repairmen had the highest mean exposure in this study, but fettlers and sand mixers also had exposure values above the cohort mean (Table 2).

Sorting the silica measurements according to their date of acquisition revealed that mean levels of airborne silica dust declined significantly over time, from 0.14 mg/m$^3$ in the 1970s to 0.073 mg/m$^3$ in the 2000s ($P < 0.0001$). Concomitantly, the median exposure to silica dust fell from 0.07 mg/m$^3$ in the 1970s to 0.028 in the 2000s (Table 2).

The mean exposure varied between 0.033 mg/m$^3$ and 0.15 mg/m$^3$ and differed somewhat between the companies that participated in this study (Table 2).

The airborne silica dust measurements presented in Table 2 were used to derive estimated exposures for all job categories in the cohort (as described in Table 1) using a Mixed Model. The resulting estimated doses for each job categories are shown in Table 3.

The estimated doses differ somewhat between jobs, but most of the variation relates to employment during the early stages of the measurement period (i.e. before and during the 1970s).

For all cases the concentration of respirable quartz derived from the mixed model based on employment duration, job title, time period, specific foundry and exposure time was expressed as an average annual exposure in mg/m$^3$. There were seven cases of sarcoidosis in total among the cohort. This number was too small to permit analysis based on different job categories and companies but the sarcoidosis where distributed across the foundries. However, four of the sarcoidosis patients were in the highest quartile for silica exposure, suggesting that exposure did increase the incidence of the disease (SIR 3.92; 95 % CI = 1.07-10.03) (Table 4).

To determine the risk of RA due to airborne silica exposure, we investigated seropositive RA and seronegative RA separately. We found a significant risk for seropositive RA (18 cases; SIR 1.70; 95 % CI = 1.01-2.69) but not for seronegative RA (12 cases; SIR 1.41; 95 % CI = 0.68-2.59).

The incidence of seropositive RA was then related to silica exposure by dividing the cohort into quartiles as previously done for sarcoidosis. Here again we observed increasing incidence with higher exposure. The risk of seropositive RA was significant (SIR 2.59; 95 % CI = 1.24-4.76) for the most

exposed group (exposure above 0.048 mg/m$^3$ per year; see Table 5). No such dose-dependent risk was observed for seronegative RA (data not shown).

## Discussion

The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure (5-8) but there is also some studies that does not show such a correlation (9). However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death.

It has been suggested that sarcoidosis might be caused by exposure to an exogenous factor in individuals who are genetically susceptible (1, 3). Our study suggests that silica may be one such an exogenous factor. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster.

Several studies have linked RA with silica exposure (9, 12, 13). The hypothesis is that some factor associated with silica exposure (and smoking) may induce an immunological response to citrullinated antigens, leading to the onset of seropositive RA (ACPA-positive RA). We also found that workers with the highest levels of silica exposure had the highest risk of seropositive RA. We lacked information on the workers' smoking habits, which could affect the prevalence of RA. However, since it is likely that all the exposure groups had similar smoking habits, this seems unlikely to affect our findings.

A potential causative mechanism of both seropositive RA and sarcoidosis is the activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance. As noted above, our results suggest that inhaled silica dust may be such a causative exogenous factor.

The strength of the study is that it draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set. Moreover, the diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires. Finally, the results were compared to data for the general Swedish population in the corresponding years, which allowed us to account for annual variation.

The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis because the diagnosis is rather unusual. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis.

It is possible that some of the sarcoidosis cases considered in this work are asymptomatic patients whose condition was only detected because silica-exposed workers are required to undergo mandatory health controls including chest X-rays, which could result in overestimation of the risk of sarcoidosis. However, because workers are required to have a health check (including an X-ray examination) before starting work in a job involving exposure to silica dust, we believe that such asymptomatic cases probably would be detected before the individual in question started working.

We therefore assume that all the sarcoidosis cases identified in this study developed after the individuals in question began working at the foundries.

The increased risk of sarcoidosis cannot be explained by the X-rays that employees in the studied occupations undergo. We saw no increased incidence of sarcoidosis among the low exposure groups, who were required to have the same number of chest X-rays as the high exposure workers. Additionally, the sarcoidosis sufferers had been working at the foundries for the same length of time as the rest of the cohort (the mean working time for both groups was 11 years) and so they would have been through the same number of X-ray examinations.

## Conclusions

Our results reveal a significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust (> 0.048 mg/m3) compared to non-exposed and less heavily exposed groups. Silica dust may thus be an exogenous factor that initiates sarcoidosis and seropositive RA in genetically predisposed individuals.

## Contributor ship

PV, ILB and PG conceived and designed the study. LA did the data collection. ILB did the main data analysis and PV, ILB and PG interpreted the results. PV, ILB and PG wrote manuscript with input from LA. All authors approved the final version.

## Competing interests

The authors have no competing interests in connection with this paper

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## Data sharing statement

No additional data are available.

## References


1. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet. 2014;383(9923):1155-67.
2. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016.
3. SwedishRespiratorySociety. National Guidelines for Treatment of Sarcoidosis. 2014.
4. Yeager H, Gopalan S, Mathew P, Lawless O, Bellanti JA. Sarcoidosis: can a murine model help define a role for silica? Med Hypotheses. 2012;78(1):36-8.
5. Sola R, Boj M, Hernandez-Flix S, Camprubi M. Silica in oral drugs as a possible sarcoidosis-inducing antigen. Lancet. 2009;373(9679):1943-4.
6. Drent M, Wijnen PA, Boots AW, Bast A. Cat litter is a possible trigger for sarcoidosis. Eur Respir J. 2012;39(1):221-2.
7. Rafnsson V, Ingimarsson O, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. Occup Environ Med. 1998;55(10):657-60.
8. Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med. 2003;60(2):122-9.
9. Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012;379(9830):2008-18.
10. Andersson L, Bryngelsson IL, Ohlson CG, Naystrom P, Lilja BG, Westberg H. Quartz and dust exposure in Swedish iron foundries. J Occup Environ Hyg. 2009;6(1):9-18.
11. SwedishWorkEnvironmentAuthority. Medical Assessment in the Workplace. 2005.
12. Stolt P, Yahya A, Bengtsson C, Kallberg H, Ronnelid J, Lundberg I, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann Rheum Dis. 2010;69(6):1072-6.
13. Perry E, Kelly C, Eggleton P, De Soyza A, Hutchinson D. The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? Rheumatology (Oxford). 2014;53(11):1940-50.
14. Westberg H, Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG. Cancer morbidity and quartz exposure in Swedish iron foundries. Int Arch Occup Environ Health. 2013;86(5):499-507.
15. Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG, Westberg H. Exposure assessment and modeling of quartz in Swedish iron foundries for a nested case-control study on lung cancer. J Occup Environ Hyg. 2012;9(2):110-9.

Table 1: General information about the cohort

| | | Number of subjects | Percent |
|---|---|---|---|
| Start of work (year) | 1930-1949 | 55 | 2.5 |
| | 1950-1969 | 425 | 19.4 |
| | 1970 – 1989 | 1 035 | 47.3 |
| | 1990+ | 672 | 30.7 |
| Years of employment | 1-<2 | 357 | 16.3 |
| | 2-10 | 936 | 42.8 |
| | 11-20 | 472 | 21.5 |
| | 20+ | 422 | 19.3 |
| Job categories | many jobs | 249 | 11.4 |
| | caster | 64 | 2.9 |
| | moulder | 209 | 9.6 |
| | core maker | 246 | 11.3 |
| | sand mixer | 7 | 0.3 |
| | melter | 131 | 6.0 |
| | furnace and ladle repair | 6 | 0.3 |
| | shake out | 18 | 1.0 |
| | fettler | 430 | 20.0 |
| | maintenance | 171 | 7.8 |
| | transportation | 26 | 1.2 |
| | other specified | 96 | 4.4 |
| | foundry workers | 196 | 9.0 |
| | office work | 48 | 2.2 |
| | other unspecified | 290 | 13.2 |

Table 2: Measurements of silica exposure for different job categories (mg/m$^3$)

| Job title | N | Mean | Median | Minimum | Maximum | Std. Deviation |
|---|---|---|---|---|---|---|
| caster | 68 | 0.033 | 0.018 | 0.0054 | 0.17 | 0.038 |
| moulder | 257 | 0.058 | 0.039 | 0.0034 | 0.98 | 0.081 |
| core maker | 171 | 0.024 | 0.017 | 0.003 | 0.19 | 0.023 |
| fettler | 573 | 0.087 | 0.039 | 0.0025 | 2.1 | 0.16 |
| sand mixer | 91 | 0.088 | 0.034 | 0.0036 | 1.1 | 0.18 |
| furnace and ladle repair | 71 | 0.42 | 0.12 | 0.0028 | 4.9 | 0.76 |
| melter | 111 | 0.052 | 0.022 | 0.0038 | 0.52 | 0.079 |
| transportation | 29 | 0.031 | 0.023 | 0.0018 | 0.11 | 0.022 |
| maintenance | 67 | 0.054 | 0.029 | 0.0052 | 0.67 | 0.09 |
| shake out | 148 | 0.079 | 0.037 | 0.0047 | 3.3 | 0.29 |
| other | 81 | 0.088 | 0.03 | 0.005 | 2.1 | 0.25 |
| | | | | | | |
| Years for measurement | | | | | | |
| 1970-1979 | 303 | 0.14 | 0.07 | 0.003 | 3.3 | 0.26 |
| 1980-1989 | 347 | 0.08 | 0.027 | 0.0036 | 4.9 | 0.31 |
| 1990-1999 | 472 | 0.062 | 0.026 | 0.0018 | 1.9 | 0.16 |
| 2000-2006 | 545 | 0.073 | 0.028 | 0.0033 | 2.1 | 0.2 |
| | | | | | | |
| Company | | | | | | |
| 1 | 135 | 0.065 | 0.044 | 0.0035 | 0.29 | 0.062 |
| 2 | 53 | 0.075 | 0.035 | 0.0054 | 0.89 | 0.14 |
| 3 | 213 | 0.088 | 0.05 | 0.0083 | 0.98 | 0.13 |
| 4 | 250 | 0.15 | 0.047 | 0.0038 | 4.9 | 0.43 |
| 6 | 58 | 0.099 | 0.024 | 0.0038 | 1.4 | 0.21 |
| 7 | 320 | 0.079 | 0.036 | 0.0018 | 2.1 | 0.21 |
| 8 | 306 | 0.063 | 0.018 | 0.0036 | 3.3 | 0.23 |
| 9 | 35 | 0.092 | 0.056 | 0.0084 | 0.28 | 0.083 |
| 10 | 174 | 0.033 | 0.027 | 0.0037 | 0.3 | 0.032 |
| 11 | 123 | 0.076 | 0.031 | 0.0033 | 0.77 | 0.12 |
| Total | 1667 | 0.083 | 0.033 | 0.0018 | 4.9 | 0.23 |

Table 3: Estimated silica dose per year (mg/m$^3$) for each job title based on a mixed model.

| | N | Mean | Median | Min | Max | Std. Deviation |
|---|---|---|---|---|---|---|
| Job title | | | | | | |
| many jobs | 249 | 0.04 | 0.039 | 0.017 | 0.12 | 0.013 |
| caster | 64 | 0.028 | 0.023 | 0.015 | 0.06 | 0.012 |
| moulder | 209 | 0.042 | 0.032 | 0.018 | 0.098 | 0.023 |
| core maker | 246 | 0.023 | 0.02 | 0.012 | 0.061 | 0.0096 |
| sand mixer | 7 | 0.068 | 0.063 | 0.052 | 0.089 | 0.016 |
| melter | 131 | 0.03 | 0.026 | 0.016 | 0.085 | 0.015 |
| furnace and ladle repair | 6 | 0.15 | 0.14 | 0.11 | 0.21 | 0.033 |
| shake out | 18 | 0.056 | 0.054 | 0.026 | 0.1 | 0.022 |
| fettler | 430 | 0.044 | 0.037 | 0.023 | 0.12 | 0.016 |
| maintenance | 171 | 0.041 | 0.036 | 0.021 | 0.077 | 0.016 |
| transportation | 26 | 0.038 | 0.044 | 0.019 | 0.059 | 0.012 |
| other specified | 96 | 0.04 | 0.036 | 0.021 | 0.089 | 0.016 |
| foundry workers | 196 | 0.056 | 0.06 | 0.024 | 0.1 | 0.017 |
| office work | 48 | 0.037 | 0.033 | 0.021 | 0.073 | 0.011 |
| other unspecified | 290 | 0.038 | 0.028 | 0.02 | 0.11 | 0.021 |

Table 4: Incidence of sarcoidosis in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| Total | 2 187 | 23 748 | 7 | 4.98 | 1.41 | 0.56-2.89 |
| 0.012 - 0.023 | 546 | 6 279 | 0 | 1.38 | - | - |
| 0.024 - 0.035 | 547 | 6 141 | 1 | 1.35 | 0.74 | 0.02-4.12 |
| 0.036 - 0.047 | 547 | 5 889 | 2 | 1.24 | 1.62 | 0.20-5.84 |
| 0.048+ | 547 | 5 439 | 4 | 1.02 | 3.942 | 1.07-10.08 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles.

Table 5: Incidence of seropositive rheumatoid arthritis (RA) in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | Person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| | 2 187 | 23 689 | 18 | 10.6 | 1.70 | 1.01-2.69 |
| 0.012 - 0.023 | 546 | 6 267 | 2 | 1.667 | 1.20 | 0.15-4.32 |
| 0.024 - 0.035 | 547 | 6 144 | 1 | 2.35 | 0.43 | 0.01-2.37 |
| 0.036 - 0.047 | 547 | 5 868 | 5 | 2.70 | 1.86 | 0.60-4.33 |
| 0.048+ | 547 | 5 410 | 10 | 3.90 | 2.59 | 1.24-4.76 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles

## Figure Legend

Figure 1: Selection of participants for inclusion in the cohort

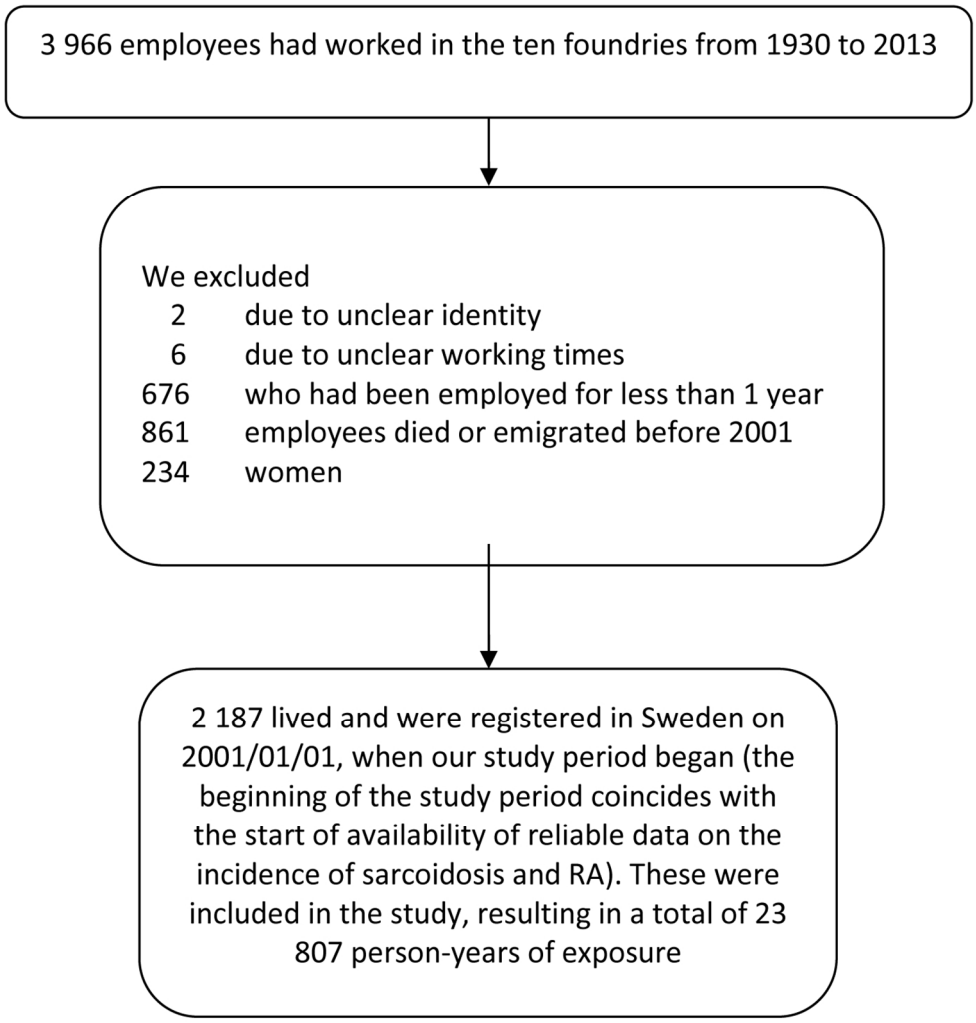


Figure 1: Selection of participants for inclusion in the cohort

121x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 | Register study |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 | The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses. Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals. |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 | Sarcoidosis has no clear etiology, although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals. One such suspected environmental factor is silica or silica dust |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 and 3 | To study the impact of occupational silica exposure on the incidence rate of sarcoidosis |

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| | | | | and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries. |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 | Data from ten iron foundries' lists of employees were available in this study. The cohort was linked to the "National non-primary outpatient care register", which is maintained by the Swedish National Board of Health and Welfare and contains data for all years since 2001. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 and figure 1 | The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded. The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment |

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| | | | | period represents 23 807 person-years at risk. |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 2, 3, 4 and 8 | Sarkodosis and RA. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).<br>Silica exposure. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *4* | The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.<br>For sarcoidosis and RA The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers |

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| | | | | of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers. |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8 | As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster. |
| Study size | 10 | Explain how the study size was arrived at | 4 and figure 1 | The foundries' (where we had silica measurements) personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded: 2 due to unclear identity, 6 due to unclear working times, 676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |

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| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4 and 5 | A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures ($mg/m^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 4 | A mixed model was used to calculate silica exposure concentrations<br>The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed |

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| | | | | numbers. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | not applicable | |
| | | (*c*) Explain how missing data were addressed | See figure 1 | Excluded individuals |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | not applicable | |
| | | (*e*) Describe any sensitivity analyses | Not done in this study | |
| **Results** | | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 | The initial cohort had 3 966 subjects, of whom 1 779 were excluded: |
| | | (b) Give reasons for non-participation at each stage | Figure 1 | 2 due to unclear identity, 6 due to unclear working times,<br>676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |
| | | (c) Consider use of a flow diagram | Given in figure 1 | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 | Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years |
| | | (b) Indicate number of participants with missing data for each variable of interest | Se figure 1 | Excluded individuals |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow- |

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| | | | | up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | *6* | There were seven cases of sarcoidosis in total among the cohort.<br>Seropositive RA; 18 cases<br>seronegative RA; 12 cases |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | not applicable | |
| | | (*b*) Report category boundaries when continuous variables were categorized | 5 | Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not possible | |

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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | none | |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 8 | The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis because the diagnosis is rather unusual. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure but there is also some studies that does not show such a correlation. However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 | Our results reveal a significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust compared to non-exposed and less heavily exposed groups. Silica dust may |

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| | | | | thus be an exogenous factor that initiates sarcoidosis and seropositive RA in genetically predisposed individuals. |
| **Other information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 9 | This study was done with support from Region Örebro County. |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure – a retrospective cohort study

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| | |

# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure – a retrospective cohort study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors.
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Region Örebro County for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work
The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Abstract

**Objective**: To study the impact of occupational silica exposure on the incidence rate of sarcoidosis and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries.

**Design**: The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses.

**Setting**: The personnel records from ten iron foundries were used to identify workers whose employment began before 2005 which was then linked to the National non-primary outpatient visits register.

**Participants**: The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. The cohort's employment period represents 23 807 person-years at risk.

**Main outcome:** The results presented in our study indicate that moderate to high levels of silica exposure increase the risk of sarcoidosis and seropositive rheumatoid arthritis.

**Results**: Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals.

**Conclusions** This study show a significant increase in the incidence rate of sarcoidosis and seropositive rheumatoid arthritis among individuals with high exposure to silica dust (> 0.048 mg/m3) compared to non-exposed and less exposed groups.

## Strengths and limitations of this study

- This study identifies one possible trigger for Sarcoidosis as well as seropositive rheumatoid arthritis.
- This study draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis as the diagnosis is rather unusual.
- As this study is a register study we have no knowledge of other exposure that can trigger rheumatoid arthritis and Sarcoidosis.

## Keywords

Sarcoidosis, Rheumatoid arthritis, Silica

## Background

Sarcoidosis is an inflammatory disease that involves the formation of granulomas, mainly in the lungs and / or intrathoracic lymph nodes, but several other organs may also be affected (1). It is diagnosed by biopsy - usually via bronchoscopy if there is lung involvement. Sarcoidosis has no clear etiology, and it is estimated that it has an annual incidence of 11.5 per 100 000 in Sweden (2). Its frequency peaks among individuals aged between 20 and 45. Although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals (1, 3). One such suspected environmental factor is silica or silica dust, but only a few studies on silica and sarcoidosis have been published. An animal study showed that the silica administered via the gastrointestinal tract or intravenously promoted granuloma development in animals infected with mycobacteria (4). Additionally, there have been reports of persistent sarcoidosis going into regression upon cessation of silica exposure (5, 6). A cohort study of workers in a limestone quarry (diatomaceous earth) in Iceland yielded a sarcoidosis incidence rate of 9.3 / 100,000, compared to a value of 0.5-2.7 / 100 000 for the Icelandic population as a whole(7). While this was taken to suggest that silica exposure may increase the risk of sarcoidosis, the sample was so small that it would be difficult to draw firm conclusions(7). A large case-control study from the US suggested that silica is associated with a range of diseases in addition to silicosis, including lung cancer, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, and the autoimmune disease rheumatoid arthritis (RA) (8). While this study did find increased risks of various autoimmune diseases (including systemic lupus erythematosus (SLE) and systemic sclerosis) with silica exposure, it did not indicate any connection with sarcoidosis.

Silica exposure is known to cause a fibrotic and potentially fatal lung disease called silicosis (9). Silicosis is currently rare in Sweden because of legislation against silica and silica dust exposure, which has successfully reduced occupational exposure levels (10). This legislation also requires people who are occupationally exposed to silica dust to undergo regular medical checks including physical examinations with spirometry and chest X-rays to ensure the absence of lung disease (11). To study the impact of occupational silica exposure on the risk of sarcoidosis, we used a cohort of silica-exposed workers from Swedish foundries (10).

As silica exposure is also suggested to be important in other inflammatory diseases such as RA (8), we also investigated the risk of RA in the studied cohort. RA and sarcoidosis are both inflammatory diseases, albeit with different symptoms. As such, the environmental factors that trigger either disease in genetically predisposed individuals may be similar (1, 12).

Earlier studies have shown that seropositive RA can be initiated within the respiratory system by autoimmune responses to citrullinated peptides (13). A Swedish cohort study found that silica exposure combined with smoking is associated with an increased risk of developing anti-citrullinated protein antibody (ACPA) positive RA (12).

At our clinic, we have recently had some patients with pulmonary sarcoidosis who also experienced occupational exposure to silica. This prompted us to investigate whether silica dust could cause sarcoidosis, and since these patients now had sarcoidosis, whether it would be advisable for them to stop their occupational exposure to silica.

## Methods and statistical analysis

Data from ten iron foundries' lists of employees were available in this study (10, 14). The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded (Figure 1). The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment period represents 23 807 person-years at risk.

All Swedish residents have a unique personal identification number and equal access to health care and hospital services. This makes it possible to retrieve patient data from a variety of registers, creating unique opportunities to analyze morbidity across the entire patient population. Such nation-wide patient registers are well suited for epidemiological studies.

The cohort was linked to the "National non-primary outpatient care register", which is maintained and validated by the Swedish National Board of Health and Welfare and contains data for all years since 2001. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).

The sarcoidosis and RA morbidity analyses covered the period from 2001 (when the National non-primary outpatient care register started) through to 2013. Information on the workers' vital status and emigration status as of the 31$^{st}$ of December 2013 were obtained from the Swedish population registry.

The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then.

The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) and RA (classified as M05 and M06 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference (derived from the "National non-primary outpatient care register"). Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers.

The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.

A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the

ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures (mg/m$^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in mg/m$^3$ and categorized into four dose groups (quartiles):<0.023 mg/m$^3$, 0.024-0.035 mg/m$^3$, 0.036-0.047 mg/m$^3$ and >0.048 mg/m$^3$. Because we lack data from before 1968, exposure times before this year were estimated based on the silica level after 1968. The exposures for the groups 'Other specified', 'Foundry workers' and 'Other unspecified' were taken to equal the mean exposure for all the other job classes. The exposure measurement database and exposure modelling are presented elsewhere (15).

## Patient involvement

No patients were involved in the design or conduct of this register study.

The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Results

Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years (Table 1). The total range for employment was 1 to 52 years and the mean length of employment was 11 years. As can be seen in Table 1, the cohort included workers representing a wide variety of job categories; the most frequent were fettler (20%) and core maker (11.3%). However, many of the workers had been employed in several different capacities during the study period (Table 1).

Silica exposure had been measured for all the job categories, and was found to vary between 0.0054-4.9 mg/m$^3$ (Table 2). The highest measurements were well above the Swedish occupational exposure limit (OEL) of 0.1 mg/m$^3$, but both the mean and median measurements for most job titles were below the OEL, with the exception of furnace and ladle repair (Table 2). Furnace and ladle repairmen had the highest mean exposure in this study, but fettlers and sand mixers also had exposure values above the cohort mean (Table 2).

Sorting the silica measurements according to their date of acquisition revealed that mean levels of airborne silica dust declined significantly over time, from 0.14 mg/m$^3$ in the 1970s to 0.073 mg/m$^3$ in the 2000s ($P < 0.0001$). Concomitantly, the median exposure to silica dust fell from 0.07 mg/m$^3$ in the 1970s to 0.028 in the 2000s (Table 2).

The mean exposure varied between 0.033 mg/m$^3$ and 0.15 mg/m$^3$ and differed somewhat between the companies that participated in this study (Table 2).

The airborne silica dust measurements presented in Table 2 were used to derive estimated exposures for all job categories in the cohort (as described in Table 1) using a Mixed Model. The resulting estimated doses for each job categories are shown in Table 3.

The estimated doses differ somewhat between jobs, but most of the variation relates to employment during the early stages of the measurement period (i.e. before and during the 1970s).

For all cases the concentration of respirable quartz derived from the mixed model based on employment duration, job title, time period, specific foundry and exposure time was expressed as an average annual exposure in mg/m$^3$. There were seven cases of sarcoidosis in total among the cohort. This number was too small to permit analysis based on different job categories and companies but the sarcoidosis where distributed across the foundries. However, four of the sarcoidosis patients were in the highest quartile for silica exposure, suggesting that exposure did increase the incidence of the disease (SIR 3.92; 95 % CI = 1.07-10.03) (Table 4).

To determine the risk of RA due to airborne silica exposure, we investigated seropositive RA and seronegative RA separately. We found a significant risk for seropositive RA (18 cases; SIR 1.70; 95 % CI = 1.01-2.69) but not for seronegative RA (12 cases; SIR 1.41; 95 % CI = 0.68-2.59).

The incidence of seropositive RA was then related to silica exposure by dividing the cohort into quartiles as previously done for sarcoidosis. Here again we observed increasing incidence with higher exposure. The risk of seropositive RA was significant (SIR 2.59; 95 % CI = 1.24-4.76) for the most

exposed group (exposure above 0.048 mg/m$^3$ per year; see Table 5). No such dose-dependent risk was observed for seronegative RA (data not shown).

## Discussion

The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure (5-8) but there is also some studies that does not show such a correlation (9). However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death.

It has been suggested that sarcoidosis might be caused by exposure to an exogenous factor in individuals who are genetically susceptible (1, 3). Our study suggests that silica may be one such an exogenous factor. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster.

Several studies have linked RA with silica exposure (9, 12, 13). The hypothesis is that some factor associated with silica exposure (and smoking) may induce an immunological response to citrullinated antigens, leading to the onset of seropositive RA (ACPA-positive RA). We also found that workers with the highest levels of silica exposure had the highest risk of seropositive RA. We lacked information on the workers' smoking habits, which could affect the prevalence of RA. However, since it is likely that all the exposure groups had similar smoking habits, this seems unlikely to affect our findings (14).

A potential causative mechanism of both seropositive RA and sarcoidosis is the activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance. As noted above, our results suggest that inhaled silica dust may be such a causative exogenous factor.

The strength of the study is that it draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set. Moreover, the diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires. Finally, the results were compared to data for the general Swedish population in the corresponding years, which allowed us to account for annual variation.

The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis.

It is possible that some of the sarcoidosis cases considered in this work are asymptomatic patients whose condition was only detected because silica-exposed workers are required to undergo mandatory health controls including chest X-rays, which could result in overestimation of the risk of sarcoidosis. However, because workers are required to have a health check (including an X-ray examination) before starting work in a job involving exposure to silica dust, we believe that such asymptomatic cases probably would be detected before the individual in question started working. We therefore assume that all the sarcoidosis cases identified in this study developed after the individuals in question began working at the foundries.

The increased risk of sarcoidosis cannot be explained by the X-rays that employees in the studied occupations undergo. We saw no increased incidence of sarcoidosis among the low exposure groups, who were required to have the same number of chest X-rays as the high exposure workers thus chest x-ray cannot explain the dos-response between high and low exposure. Additionally, the sarcoidosis sufferers had been working at the foundries for the same length of time as the rest of the cohort (the mean working time for both groups was 11 years) and so they would have been through the same number of X-ray examinations.

## Conclusions

Our results reveal a significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust (> 0.048 mg/m3) compared to non-exposed and less heavily exposed groups.

## Contributor ship

PV, ILB and PG conceived and designed the study. LA did the data collection. ILB did the main data analysis and PV, ILB and PG interpreted the results. PV, ILB and PG wrote manuscript with input from LA. All authors approved the final version.

## Competing interests

The authors have no competing interests in connection with this paper

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This study was done with support from Region Örebro County (OLL-554311).

## Data sharing statement

No additional data are available.

## References

1. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet. 2014;383(9923):1155-67.
2. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016.
3. SwedishRespiratorySociety. National Guidelines for Treatment of Sarcoidosis. 2014.
4. Yeager H, Gopalan S, Mathew P, Lawless O, Bellanti JA. Sarcoidosis: can a murine model help define a role for silica? Med Hypotheses. 2012;78(1):36-8.
5. Sola R, Boj M, Hernandez-Flix S, Camprubi M. Silica in oral drugs as a possible sarcoidosis-inducing antigen. Lancet. 2009;373(9679):1943-4.
6. Drent M, Wijnen PA, Boots AW, Bast A. Cat litter is a possible trigger for sarcoidosis. Eur Respir J. 2012;39(1):221-2.
7. Rafnsson V, Ingimarsson O, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. Occup Environ Med. 1998;55(10):657-60.
8. Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med. 2003;60(2):122-9.
9. Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012;379(9830):2008-18.
10. Andersson L, Bryngelsson IL, Ohlson CG, Naystrom P, Lilja BG, Westberg H. Quartz and dust exposure in Swedish iron foundries. J Occup Environ Hyg. 2009;6(1):9-18.
11. SwedishWorkEnvironmentAuthority. Medical Assessment in the Workplace. 2005.
12. Stolt P, Yahya A, Bengtsson C, Kallberg H, Ronnelid J, Lundberg I, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann Rheum Dis. 2010;69(6):1072-6.
13. Perry E, Kelly C, Eggleton P, De Soyza A, Hutchinson D. The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? Rheumatology (Oxford). 2014;53(11):1940-50.
14. Westberg H, Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG. Cancer morbidity and quartz exposure in Swedish iron foundries. Int Arch Occup Environ Health. 2013;86(5):499-507.
15. Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG, Westberg H. Exposure assessment and modeling of quartz in Swedish iron foundries for a nested case-control study on lung cancer. J Occup Environ Hyg. 2012;9(2):110-9.

Table 1: General information about the cohort

| | | Number of subjects | Percent |
|---|---|---|---|
| Start of work (year) | 1930-1949 | 55 | 2.5 |
| | 1950-1969 | 425 | 19.4 |
| | 1970 – 1989 | 1 035 | 47.3 |
| | 1990+ | 672 | 30.7 |
| Years of employment | 1-<2 | 357 | 16.3 |
| | 2-10 | 936 | 42.8 |
| | 11-20 | 472 | 21.5 |
| | 20+ | 422 | 19.3 |
| Job categories | many jobs | 249 | 11.4 |
| | caster | 64 | 2.9 |
| | moulder | 209 | 9.6 |
| | core maker | 246 | 11.3 |
| | sand mixer | 7 | 0.3 |
| | melter | 131 | 6.0 |
| | furnace and ladle repair | 6 | 0.3 |
| | shake out | 18 | 1.0 |
| | fettler | 430 | 20.0 |
| | maintenance | 171 | 7.8 |
| | transportation | 26 | 1.2 |
| | other specified | 96 | 4.4 |
| | foundry workers | 196 | 9.0 |
| | office work | 48 | 2.2 |
| | other unspecified | 290 | 13.2 |

Table 2: Measurements of silica exposure for different job categories (mg/m$^3$)

| Job title | N | Mean | Median | Minimum | Maximum | Std. Deviation |
|---|---|---|---|---|---|---|
| caster | 68 | 0.033 | 0.018 | 0.0054 | 0.17 | 0.038 |
| moulder | 257 | 0.058 | 0.039 | 0.0034 | 0.98 | 0.081 |
| core maker | 171 | 0.024 | 0.017 | 0.003 | 0.19 | 0.023 |
| fettler | 573 | 0.087 | 0.039 | 0.0025 | 2.1 | 0.16 |
| sand mixer | 91 | 0.088 | 0.034 | 0.0036 | 1.1 | 0.18 |
| furnace and ladle repair | 71 | 0.42 | 0.12 | 0.0028 | 4.9 | 0.76 |
| melter | 111 | 0.052 | 0.022 | 0.0038 | 0.52 | 0.079 |
| transportation | 29 | 0.031 | 0.023 | 0.0018 | 0.11 | 0.022 |
| maintenance | 67 | 0.054 | 0.029 | 0.0052 | 0.67 | 0.09 |
| shake out | 148 | 0.079 | 0.037 | 0.0047 | 3.3 | 0.29 |
| other | 81 | 0.088 | 0.03 | 0.005 | 2.1 | 0.25 |
| | | | | | | |
| Years for measurement | | | | | | |
| 1970-1979 | 303 | 0.14 | 0.07 | 0.003 | 3.3 | 0.26 |
| 1980-1989 | 347 | 0.08 | 0.027 | 0.0036 | 4.9 | 0.31 |
| 1990-1999 | 472 | 0.062 | 0.026 | 0.0018 | 1.9 | 0.16 |
| 2000-2006 | 545 | 0.073 | 0.028 | 0.0033 | 2.1 | 0.2 |
| | | | | | | |
| Company | | | | | | |
| 1 | 135 | 0.065 | 0.044 | 0.0035 | 0.29 | 0.062 |
| 2 | 53 | 0.075 | 0.035 | 0.0054 | 0.89 | 0.14 |
| 3 | 213 | 0.088 | 0.05 | 0.0083 | 0.98 | 0.13 |
| 4 | 250 | 0.15 | 0.047 | 0.0038 | 4.9 | 0.43 |
| 6 | 58 | 0.099 | 0.024 | 0.0038 | 1.4 | 0.21 |
| 7 | 320 | 0.079 | 0.036 | 0.0018 | 2.1 | 0.21 |
| 8 | 306 | 0.063 | 0.018 | 0.0036 | 3.3 | 0.23 |
| 9 | 35 | 0.092 | 0.056 | 0.0084 | 0.28 | 0.083 |
| 10 | 174 | 0.033 | 0.027 | 0.0037 | 0.3 | 0.032 |
| 11 | 123 | 0.076 | 0.031 | 0.0033 | 0.77 | 0.12 |
| Total | 1667 | 0.083 | 0.033 | 0.0018 | 4.9 | 0.23 |

Table 3: Estimated silica dose per year (mg/m$^3$) for each job title based on a mixed model.

| | N | Mean | Median | Min | Max | Std. Deviation |
|---|---|---|---|---|---|---|
| Job title | | | | | | |
| many jobs | 249 | 0.04 | 0.039 | 0.017 | 0.12 | 0.013 |
| caster | 64 | 0.028 | 0.023 | 0.015 | 0.06 | 0.012 |
| moulder | 209 | 0.042 | 0.032 | 0.018 | 0.098 | 0.023 |
| core maker | 246 | 0.023 | 0.02 | 0.012 | 0.061 | 0.0096 |
| sand mixer | 7 | 0.068 | 0.063 | 0.052 | 0.089 | 0.016 |
| melter | 131 | 0.03 | 0.026 | 0.016 | 0.085 | 0.015 |
| furnace and ladle repair | 6 | 0.15 | 0.14 | 0.11 | 0.21 | 0.033 |
| shake out | 18 | 0.056 | 0.054 | 0.026 | 0.1 | 0.022 |
| fettler | 430 | 0.044 | 0.037 | 0.023 | 0.12 | 0.016 |
| maintenance | 171 | 0.041 | 0.036 | 0.021 | 0.077 | 0.016 |
| transportation | 26 | 0.038 | 0.044 | 0.019 | 0.059 | 0.012 |
| other specified | 96 | 0.04 | 0.036 | 0.021 | 0.089 | 0.016 |
| foundry workers | 196 | 0.056 | 0.06 | 0.024 | 0.1 | 0.017 |
| office work | 48 | 0.037 | 0.033 | 0.021 | 0.073 | 0.011 |
| other unspecified | 290 | 0.038 | 0.028 | 0.02 | 0.11 | 0.021 |

Table 4: Incidence of sarcoidosis in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| Total | 2 187 | 23 748 | 7 | 4.98 | 1.41 | 0.56-2.89 |
| 0.012 - 0.023 | 546 | 6 279 | 0 | 1.38 | - | - |
| 0.024 - 0.035 | 547 | 6 141 | 1 | 1.35 | 0.74 | 0.02-4.12 |
| 0.036 - 0.047 | 547 | 5 889 | 2 | 1.24 | 1.62 | 0.20-5.84 |
| 0.048+ | 547 | 5 439 | 4 | 1.02 | 3.942 | 1.07-10.08 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles.

Table 5: Incidence of seropositive rheumatoid arthritis (RA) in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | Person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| | 2 187 | 23 689 | 18 | 10.6 | 1.70 | 1.01-2.69 |
| 0.012 - 0.023 | 546 | 6 267 | 2 | 1.667 | 1.20 | 0.15-4.32 |
| 0.024 - 0.035 | 547 | 6 144 | 1 | 2.35 | 0.43 | 0.01-2.37 |
| 0.036 - 0.047 | 547 | 5 868 | 5 | 2.70 | 1.86 | 0.60-4.33 |
| 0.048+ | 547 | 5 410 | 10 | 3.90 | 2.59 | 1.24-4.76 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles

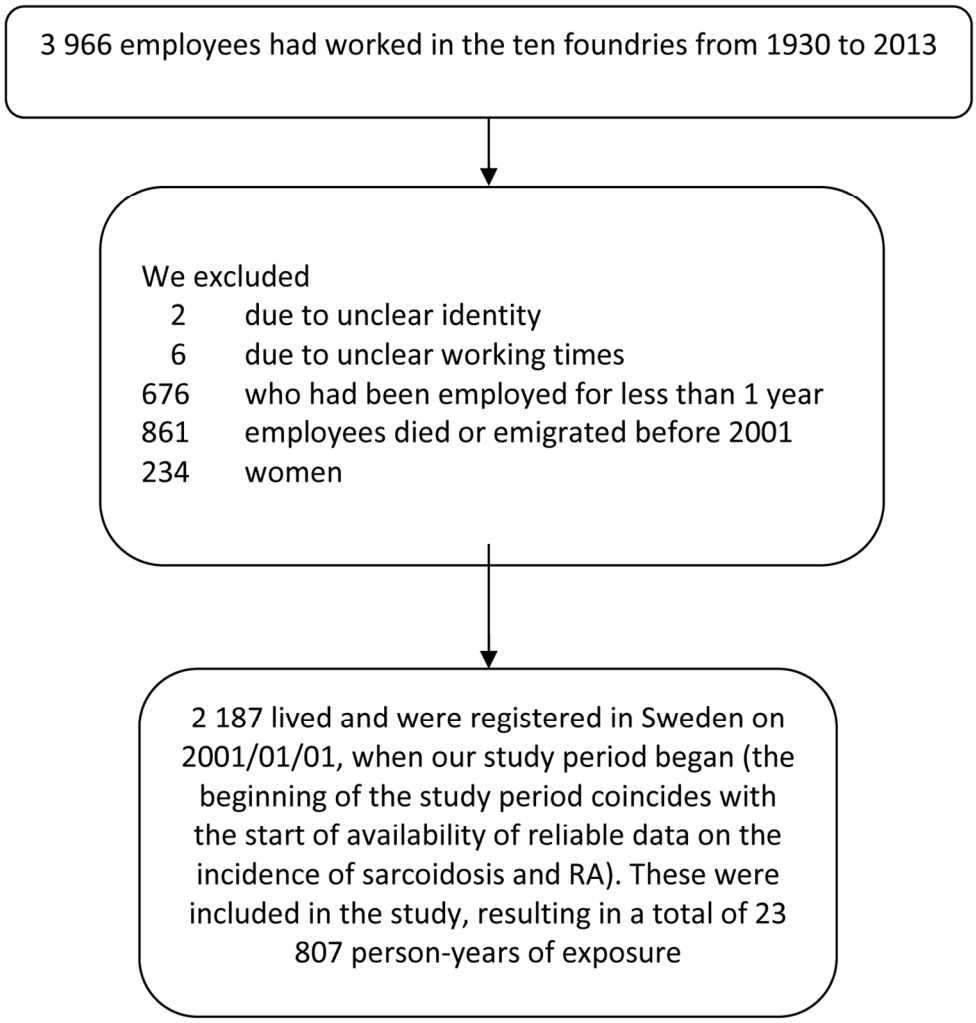


Figure 1: Selection of participants for inclusion in the cohort

121x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 | Register study |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 | The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses. Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals. |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 | Sarcoidosis has no clear etiology, although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals. One such suspected environmental factor is silica or silica dust |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 and 3 | To study the impact of occupational silica exposure on the incidence rate of sarcoidosis |

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|---|---|---|---|---|
| | | | | and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries. |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 | Data from ten iron foundries' lists of employees were available in this study. The cohort was linked to the "National non-primary outpatient care register", which is maintained by the Swedish National Board of Health and Welfare and contains data for all years since 2001. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 and figure 1 | The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded. The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment |

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|---|---|---|---|---|
| | | | | period represents 23 807 person-years at risk. |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 2, 3, 4 and 8 | Sarkodosis and RA. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).<br>Silica exposure. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *4* | The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.<br>For sarcoidosis and RA The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers |

| | | | | |
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| | | | | of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers. |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8 | As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster. |
| Study size | 10 | Explain how the study size was arrived at | 4 and figure 1 | The foundries' (where we had silica measurements) personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded: 2 due to unclear identity, 6 due to unclear working times, 676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |

Continued on next page

| | | | | |
|---|---|---|---|---|
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4 and 5 | A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures ($mg/m^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 4 | A mixed model was used to calculate silica exposure concentrations<br>The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed |

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| | | | | numbers. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | not applicable | |
| | | (*c*) Explain how missing data were addressed | See figure 1 | Excluded individuals |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | not applicable | |
| | | (*e*) Describe any sensitivity analyses | Not done in this study | |
| **Results** | | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 | The initial cohort had 3 966 subjects, of whom 1 779 were excluded: |
| | | (b) Give reasons for non-participation at each stage | Figure 1 | 2 due to unclear identity, 6 due to unclear working times,<br>676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |
| | | (c) Consider use of a flow diagram | Given in figure 1 | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 | Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years |
| | | (b) Indicate number of participants with missing data for each variable of interest | Se figure 1 | Excluded individuals |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow- |

| | | | | |
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| | | | | up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | *6* | There were seven cases of sarcoidosis in total among the cohort.<br>Seropositive RA; 18 cases<br>seronegative RA; 12 cases |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | not applicable | |
| | | (*b*) Report category boundaries when continuous variables were categorized | 5 | Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not possible | |

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| | | | | |
|---|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | none | |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 8 | The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis because the diagnosis is rather unusual. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure but there is also some studies that does not show such a correlation. However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 | Our results reveal a significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust compared to non-exposed and less heavily exposed groups. Silica dust may |

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| | | | | thus be an exogenous factor that initiates sarcoidosis and seropositive RA in genetically predisposed individuals. |
| **Other information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 9 | This study was done with support from Region Örebro County. |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure – a retrospective cohort study



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| | |

# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure – a retrospective cohort study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors.
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Region Örebro County for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work
The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Abstract

**Objective**: To study the impact of occupational silica exposure on the incidence rate of sarcoidosis and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries.

**Design**: The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses.

**Setting**: The personnel records from ten iron foundries were used to identify workers whose employment began before 2005 which was then linked to the National non-primary outpatient visits register.

**Participants**: The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. The cohort's employment period represents 23 807 person-years at risk.

**Main outcome:** The results presented in our study indicate that moderate to high levels of silica exposure increase the risk of sarcoidosis and seropositive rheumatoid arthritis.

**Results**: Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals.

**Conclusions** This study show a statistically significant increase in the incidence rate of sarcoidosis and seropositive rheumatoid arthritis among individuals with high exposure to silica dust (> 0.048 mg/m3) compared to non-exposed and less exposed groups.


## Strengths and limitations of this study

- This study identifies one possible trigger for Sarcoidosis as well as seropositive rheumatoid arthritis.
- This study draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis as the diagnosis is rather unusual.
- As this study is a register study we have no knowledge of other exposure that can trigger rheumatoid arthritis and Sarcoidosis.


## Keywords

Sarcoidosis, Rheumatoid arthritis, Silica

## Background

Sarcoidosis is an inflammatory disease that involves the formation of granulomas, mainly in the lungs and / or intrathoracic lymph nodes, but several other organs may also be affected (1). It is diagnosed by biopsy - usually via bronchoscopy if there is lung involvement. Sarcoidosis has no clear etiology, and it is estimated that it has an annual incidence of 11.5 per 100 000 in Sweden (2). Its frequency peaks among individuals aged between 20 and 45. Although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals (1, 3). One such suspected environmental factor is silica or silica dust, but only a few studies on silica and sarcoidosis have been published. An animal study showed that the silica administered via the gastrointestinal tract or intravenously promoted granuloma development in animals infected with mycobacteria (4). Additionally, there have been reports of persistent sarcoidosis going into regression upon cessation of silica exposure (5, 6). A cohort study of workers in a limestone quarry (diatomaceous earth) in Iceland yielded a sarcoidosis incidence rate of 9.3 / 100,000, compared to a value of 0.5-2.7 / 100 000 for the Icelandic population as a whole(7). While this was taken to suggest that silica exposure may increase the risk of sarcoidosis, the sample was so small that it would be difficult to draw firm conclusions(7). A large case-control study from the US suggested that silica is associated with a range of diseases in addition to silicosis, including lung cancer, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, and the autoimmune disease rheumatoid arthritis (RA) (8). While this study did find increased risks of various autoimmune diseases (including systemic lupus erythematosus (SLE) and systemic sclerosis) with silica exposure, it did not indicate any connection with sarcoidosis.

Silica exposure is known to cause a fibrotic and potentially fatal lung disease called silicosis (9). Silicosis is currently rare in Sweden because of legislation against silica and silica dust exposure, which has successfully reduced occupational exposure levels (10). This legislation also requires people who are occupationally exposed to silica dust to undergo regular medical checks including physical examinations with spirometry and chest X-rays to ensure the absence of lung disease (11). To study the impact of occupational silica exposure on the risk of sarcoidosis, we used a cohort of silica-exposed workers from Swedish foundries (10).

As silica exposure is also suggested to be important in other inflammatory diseases such as RA (8), we also investigated the risk of RA in the studied cohort. RA and sarcoidosis are both inflammatory diseases, albeit with different symptoms. As such, the environmental factors that trigger either disease in genetically predisposed individuals may be similar (1, 12).

Earlier studies have shown that seropositive RA can be initiated within the respiratory system by autoimmune responses to citrullinated peptides (13). A Swedish cohort study found that silica exposure combined with smoking is associated with an increased risk of developing anti-citrullinated protein antibody (ACPA) positive RA (12).

At our clinic, we have recently had some patients with pulmonary sarcoidosis who also experienced occupational exposure to silica. This prompted us to investigate whether silica dust could cause sarcoidosis, and since these patients now had sarcoidosis, whether it would be advisable for them to stop their occupational exposure to silica.

## Methods and statistical analysis

Data from ten iron foundries' lists of employees were available in this study (10, 14). The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded (Figure 1). The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment period represents 23 807 person-years at risk.

All Swedish residents have a unique personal identification number and equal access to health care and hospital services. This makes it possible to retrieve patient data from a variety of registers, creating unique opportunities to analyze morbidity across the entire patient population. Such nation-wide patient registers are well suited for epidemiological studies.

The cohort was linked to the "National non-primary outpatient care register", which is maintained and validated by the Swedish National Board of Health and Welfare and contains data for all years since 2001. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).

The sarcoidosis and RA morbidity analyses covered the period from 2001 (when the National non-primary outpatient care register started) through to 2013. Information on the workers' vital status and emigration status as of the 31$^{st}$ of December 2013 were obtained from the Swedish population registry.

The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then.

The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) and RA (classified as M05 and M06 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference (derived from the "National non-primary outpatient care register"). Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers.

The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.

A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the

ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures (mg/m$^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in mg/m$^3$ and categorized into four dose groups (quartiles):<0.023 mg/m$^3$, 0.024-0.035 mg/m$^3$, 0.036-0.047 mg/m$^3$ and >0.048 mg/m$^3$. Because we lack data from before 1968, exposure times before this year were estimated based on the silica level after 1968. The exposures for the groups 'Other specified', 'Foundry workers' and 'Other unspecified' were taken to equal the mean exposure for all the other job classes. The exposure measurement database and exposure modelling are presented elsewhere (15).

## Patient involvement

No patients were involved in the design or conduct of this register study.

The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Results

Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years (Table 1). The total range for employment was 1 to 52 years and the mean length of employment was 11 years. As can be seen in Table 1, the cohort included workers representing a wide variety of job categories; the most frequent were fettler (20%) and core maker (11.3%). However, many of the workers had been employed in several different capacities during the study period (Table 1).

Silica exposure had been measured for all the job categories, and was found to vary between 0.0054-4.9 mg/m$^3$ (Table 2). The highest measurements were well above the Swedish occupational exposure limit (OEL) of 0.1 mg/m$^3$, but both the mean and median measurements for most job titles were below the OEL, with the exception of furnace and ladle repair (Table 2). Furnace and ladle repairmen had the highest mean exposure in this study, but fettlers and sand mixers also had exposure values above the cohort mean (Table 2).

Sorting the silica measurements according to their date of acquisition revealed that mean levels of airborne silica dust declined significantly over time, from 0.14 mg/m$^3$ in the 1970s to 0.073 mg/m$^3$ in the 2000s ($P < 0.0001$). Concomitantly, the median exposure to silica dust fell from 0.07 mg/m$^3$ in the 1970s to 0.028 in the 2000s (Table 2).

The mean exposure varied between 0.033 mg/m$^3$ and 0.15 mg/m$^3$ and differed somewhat between the companies that participated in this study (Table 2).

The airborne silica dust measurements presented in Table 2 were used to derive estimated exposures for all job categories in the cohort (as described in Table 1) using a Mixed Model. The resulting estimated doses for each job categories are shown in Table 3.

The estimated doses differ somewhat between jobs, but most of the variation relates to employment during the early stages of the measurement period (i.e. before and during the 1970s).

For all cases the concentration of respirable quartz derived from the mixed model based on employment duration, job title, time period, specific foundry and exposure time was expressed as an average annual exposure in mg/m$^3$. There were seven cases of sarcoidosis in total among the cohort. This number was too small to permit analysis based on different job categories and companies but the sarcoidosis where distributed across the foundries. However, four of the sarcoidosis patients were in the highest quartile for silica exposure, suggesting that exposure did increase the incidence of the disease (SIR 3.92; 95 % CI = 1.07-10.03) (Table 4).

The risk of RA due to airborne silica exposure in our cohort was increased: 1.52 (95% CI 1.00 - 2.21). When we investigated seropositive RA and seronegative RA separately. We found a statistically significant risk for seropositive RA (18 cases; SIR 1.70; 95 % CI = 1.01-2.69) but for seronegative RA the risk was not statistically significant (12 cases; SIR 1.41; 95 % CI = 0.68-2.59).

The incidence of seropositive RA was then related to silica exposure by dividing the cohort into quartiles as previously done for sarcoidosis. Here again we observed increasing incidence with higher exposure. The risk of seropositive RA was significant (SIR 2.59; 95 % CI = 1.24-4.76) for the most

exposed group (exposure above 0.048 mg/m$^3$ per year; see Table 5). No such dose-dependent risk was observed for seronegative RA (data not shown).

## Discussion

The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure (5-8) but there is also some studies that does not show such a correlation (9). However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death.

It has been suggested that sarcoidosis might be caused by exposure to an exogenous factor in individuals who are genetically susceptible (1, 3). Our study suggests that silica may be one such an exogenous factor. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster.

Several studies have linked RA with silica exposure (9, 12, 13). The hypothesis is that some factor associated with silica exposure (and smoking) may induce an immunological response to citrullinated antigens, leading to the onset of seropositive RA (ACPA-positive RA). We also found that workers with the highest levels of silica exposure had the highest risk of seropositive RA. We lack complete information on the workers' smoking habits, but as the prevalence of smoking as well as the silica exposure has decreased over time there might be a higher prevalence of smokers in the high exposed group, which could affect the prevalence of RA.

A potential causative mechanism of both seropositive RA and sarcoidosis is the activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance. As noted above, our results suggest that inhaled silica dust may be such a causative exogenous factor.

The strength of the study is that it draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set. Moreover, the diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires. Finally, the results were compared to data for the general Swedish population in the corresponding years, which allowed us to account for annual variation.

The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis.

It is possible that some of the sarcoidosis cases considered in this work are asymptomatic patients whose condition was only detected because silica-exposed workers are required to undergo mandatory health controls including chest X-rays, which could result in overestimation of the risk of sarcoidosis. However, because workers are required to have a health check (including an X-ray examination) before starting work in a job involving exposure to silica dust, we believe that such asymptomatic cases probably would be detected before the individual in question started working. We therefore assume that all the sarcoidosis cases identified in this study developed after the individuals in question began working at the foundries.

The increased risk of sarcoidosis cannot be explained by the X-rays that employees in the studied occupations undergo. We saw no increased incidence of sarcoidosis among the low exposure groups, who were required to have the same number of chest X-rays as the high exposure workers thus chest x-ray cannot explain the dos-response between high and low exposure. Additionally, the sarcoidosis sufferers had been working at the foundries for the same length of time as the rest of the cohort (the mean working time for both groups was 11 years) and so they would have been through the same number of X-ray examinations.

## Conclusions

Our results reveal a statistically significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust (> 0.048 mg/m3) compared to non-exposed and less heavily exposed groups.

## Contributor ship

PV, ILB and PG conceived and designed the study. LA did the data collection. ILB did the main data analysis and PV, ILB and PG interpreted the results. PV, ILB and PG wrote manuscript with input from LA. All authors approved the final version.

## Competing interests

The authors have no competing interests in connection with this paper

## Funding

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## Data sharing statement

No additional data are available.

## References


1. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet. 2014;383(9923):1155-67.
2. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016.
3. SwedishRespiratorySociety. National Guidelines for Treatment of Sarcoidosis. 2014.
4. Yeager H, Gopalan S, Mathew P, Lawless O, Bellanti JA. Sarcoidosis: can a murine model help define a role for silica? Med Hypotheses. 2012;78(1):36-8.
5. Sola R, Boj M, Hernandez-Flix S, Camprubi M. Silica in oral drugs as a possible sarcoidosis-inducing antigen. Lancet. 2009;373(9679):1943-4.
6. Drent M, Wijnen PA, Boots AW, Bast A. Cat litter is a possible trigger for sarcoidosis. Eur Respir J. 2012;39(1):221-2.
7. Rafnsson V, Ingimarsson O, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. Occup Environ Med. 1998;55(10):657-60.
8. Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med. 2003;60(2):122-9.
9. Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012;379(9830):2008-18.
10. Andersson L, Bryngelsson IL, Ohlson CG, Naystrom P, Lilja BG, Westberg H. Quartz and dust exposure in Swedish iron foundries. J Occup Environ Hyg. 2009;6(1):9-18.
11. SwedishWorkEnvironmentAuthority. Medical Assessment in the Workplace. 2005.
12. Stolt P, Yahya A, Bengtsson C, Kallberg H, Ronnelid J, Lundberg I, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann Rheum Dis. 2010;69(6):1072-6.
13. Perry E, Kelly C, Eggleton P, De Soyza A, Hutchinson D. The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? Rheumatology (Oxford). 2014;53(11):1940-50.
14. Westberg H, Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG. Cancer morbidity and quartz exposure in Swedish iron foundries. Int Arch Occup Environ Health. 2013;86(5):499-507.
15. Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG, Westberg H. Exposure assessment and modeling of quartz in Swedish iron foundries for a nested case-control study on lung cancer. J Occup Environ Hyg. 2012;9(2):110-9.

Table 1: General information about the cohort

| | | Number of subjects | Percent |
|---|---|---|---|
| Start of work (year) | 1930-1949 | 55 | 2.5 |
| | 1950-1969 | 425 | 19.4 |
| | 1970 – 1989 | 1 035 | 47.3 |
| | 1990+ | 672 | 30.7 |
| Years of employment | 1-<2 | 357 | 16.3 |
| | 2-10 | 936 | 42.8 |
| | 11-20 | 472 | 21.5 |
| | 20+ | 422 | 19.3 |
| Job categories | many jobs | 249 | 11.4 |
| | caster | 64 | 2.9 |
| | moulder | 209 | 9.6 |
| | core maker | 246 | 11.3 |
| | sand mixer | 7 | 0.3 |
| | melter | 131 | 6.0 |
| | furnace and ladle repair | 6 | 0.3 |
| | shake out | 18 | 1.0 |
| | fettler | 430 | 20.0 |
| | maintenance | 171 | 7.8 |
| | transportation | 26 | 1.2 |
| | other specified | 96 | 4.4 |
| | foundry workers | 196 | 9.0 |
| | office work | 48 | 2.2 |
| | other unspecified | 290 | 13.2 |

Table 2: Measurements of silica exposure for different job categories (mg/m$^3$)

| Job title | N | Mean | Median | Minimum | Maximum | Std. Deviation |
|---|---|---|---|---|---|---|
| caster | 68 | 0.033 | 0.018 | 0.0054 | 0.17 | 0.038 |
| moulder | 257 | 0.058 | 0.039 | 0.0034 | 0.98 | 0.081 |
| core maker | 171 | 0.024 | 0.017 | 0.003 | 0.19 | 0.023 |
| fettler | 573 | 0.087 | 0.039 | 0.0025 | 2.1 | 0.16 |
| sand mixer | 91 | 0.088 | 0.034 | 0.0036 | 1.1 | 0.18 |
| furnace and ladle repair | 71 | 0.42 | 0.12 | 0.0028 | 4.9 | 0.76 |
| melter | 111 | 0.052 | 0.022 | 0.0038 | 0.52 | 0.079 |
| transportation | 29 | 0.031 | 0.023 | 0.0018 | 0.11 | 0.022 |
| maintenance | 67 | 0.054 | 0.029 | 0.0052 | 0.67 | 0.09 |
| shake out | 148 | 0.079 | 0.037 | 0.0047 | 3.3 | 0.29 |
| other | 81 | 0.088 | 0.03 | 0.005 | 2.1 | 0.25 |
| | | | | | | |
| Years for measurement | | | | | | |
| 1970-1979 | 303 | 0.14 | 0.07 | 0.003 | 3.3 | 0.26 |
| 1980-1989 | 347 | 0.08 | 0.027 | 0.0036 | 4.9 | 0.31 |
| 1990-1999 | 472 | 0.062 | 0.026 | 0.0018 | 1.9 | 0.16 |
| 2000-2006 | 545 | 0.073 | 0.028 | 0.0033 | 2.1 | 0.2 |
| | | | | | | |
| Company | | | | | | |
| 1 | 135 | 0.065 | 0.044 | 0.0035 | 0.29 | 0.062 |
| 2 | 53 | 0.075 | 0.035 | 0.0054 | 0.89 | 0.14 |
| 3 | 213 | 0.088 | 0.05 | 0.0083 | 0.98 | 0.13 |
| 4 | 250 | 0.15 | 0.047 | 0.0038 | 4.9 | 0.43 |
| 6 | 58 | 0.099 | 0.024 | 0.0038 | 1.4 | 0.21 |
| 7 | 320 | 0.079 | 0.036 | 0.0018 | 2.1 | 0.21 |
| 8 | 306 | 0.063 | 0.018 | 0.0036 | 3.3 | 0.23 |
| 9 | 35 | 0.092 | 0.056 | 0.0084 | 0.28 | 0.083 |
| 10 | 174 | 0.033 | 0.027 | 0.0037 | 0.3 | 0.032 |
| 11 | 123 | 0.076 | 0.031 | 0.0033 | 0.77 | 0.12 |
| Total | 1667 | 0.083 | 0.033 | 0.0018 | 4.9 | 0.23 |

Table 3: Estimated silica dose per year (mg/m$^3$) for each job title based on a mixed model.

| | N | Mean | Median | Min | Max | Std. Deviation |
|---|---|---|---|---|---|---|
| Job title | | | | | | |
| many jobs | 249 | 0.04 | 0.039 | 0.017 | 0.12 | 0.013 |
| caster | 64 | 0.028 | 0.023 | 0.015 | 0.06 | 0.012 |
| moulder | 209 | 0.042 | 0.032 | 0.018 | 0.098 | 0.023 |
| core maker | 246 | 0.023 | 0.02 | 0.012 | 0.061 | 0.0096 |
| sand mixer | 7 | 0.068 | 0.063 | 0.052 | 0.089 | 0.016 |
| melter | 131 | 0.03 | 0.026 | 0.016 | 0.085 | 0.015 |
| furnace and ladle repair | 6 | 0.15 | 0.14 | 0.11 | 0.21 | 0.033 |
| shake out | 18 | 0.056 | 0.054 | 0.026 | 0.1 | 0.022 |
| fettler | 430 | 0.044 | 0.037 | 0.023 | 0.12 | 0.016 |
| maintenance | 171 | 0.041 | 0.036 | 0.021 | 0.077 | 0.016 |
| transportation | 26 | 0.038 | 0.044 | 0.019 | 0.059 | 0.012 |
| other specified | 96 | 0.04 | 0.036 | 0.021 | 0.089 | 0.016 |
| foundry workers | 196 | 0.056 | 0.06 | 0.024 | 0.1 | 0.017 |
| office work | 48 | 0.037 | 0.033 | 0.021 | 0.073 | 0.011 |
| other unspecified | 290 | 0.038 | 0.028 | 0.02 | 0.11 | 0.021 |

Table 4: Incidence of sarcoidosis in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| Total | 2 187 | 23 748 | 7 | 4.98 | 1.41 | 0.56-2.89 |
| 0.012 - 0.023 | 546 | 6 279 | 0 | 1.38 | - | - |
| 0.024 - 0.035 | 547 | 6 141 | 1 | 1.35 | 0.74 | 0.02-4.12 |
| 0.036 - 0.047 | 547 | 5 889 | 2 | 1.24 | 1.62 | 0.20-5.84 |
| 0.048+ | 547 | 5 439 | 4 | 1.02 | 3.942 | 1.07-10.08 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles.

Table 5: Incidence of seropositive rheumatoid arthritis (RA) in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | Person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| | 2 187 | 23 689 | 18 | 10.6 | 1.70 | 1.01-2.69 |
| 0.012 - 0.023 | 546 | 6 267 | 2 | 1.667 | 1.20 | 0.15-4.32 |
| 0.024 - 0.035 | 547 | 6 144 | 1 | 2.35 | 0.43 | 0.01-2.37 |
| 0.036 - 0.047 | 547 | 5 868 | 5 | 2.70 | 1.86 | 0.60-4.33 |
| 0.048+ | 547 | 5 410 | 10 | 3.90 | 2.59 | 1.24-4.76 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles

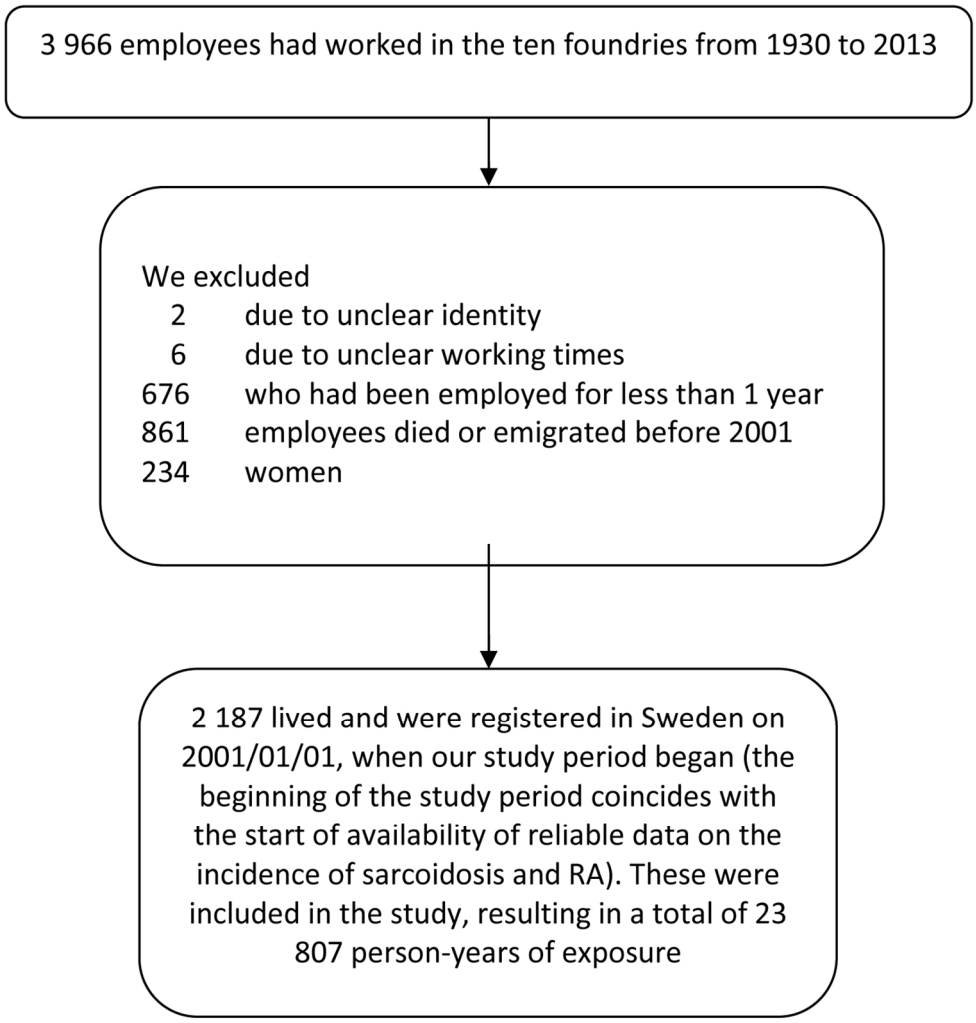


Figure 1: Selection of participants for inclusion in the cohort

121x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 | Register study |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 | The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses. Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals. |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 | Sarcoidosis has no clear etiology, although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals. One such suspected environmental factor is silica or silica dust |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 and 3 | To study the impact of occupational silica exposure on the incidence rate of sarcoidosis |

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|---|---|---|---|---|
| | | | | and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries. |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 | Data from ten iron foundries' lists of employees were available in this study. The cohort was linked to the "National non-primary outpatient care register", which is maintained by the Swedish National Board of Health and Welfare and contains data for all years since 2001. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 and figure 1 | The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded. The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment |

| | | | | |
|---|---|---|---|---|
| | | | | period represents 23 807 person-years at risk. |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 2, 3, 4 and 8 | Sarkodosis and RA. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).<br>Silica exposure. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *4* | The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.<br>For sarcoidosis and RA The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers |

| | | | | |
|---|---|---|---|---|
| | | | | of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers. |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8 | As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster. |
| Study size | 10 | Explain how the study size was arrived at | 4 and figure 1 | The foundries' (where we had silica measurements) personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded: 2 due to unclear identity, 6 due to unclear working times, 676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |

Continued on next page

| | | | | |
|---|---|---|---|---|
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4 and 5 | A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures ($mg/m^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 4 | A mixed model was used to calculate silica exposure concentrations<br>The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed |

| | | | | |
|---|---|---|---|---|
| | | | | numbers. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | not applicable | |
| | | (*c*) Explain how missing data were addressed | See figure 1 | Excluded individuals |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | not applicable | |
| | | (*e*) Describe any sensitivity analyses | Not done in this study | |
| **Results** | | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 | The initial cohort had 3 966 subjects, of whom 1 779 were excluded: |
| | | (b) Give reasons for non-participation at each stage | Figure 1 | 2 due to unclear identity, 6 due to unclear working times,<br>676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |
| | | (c) Consider use of a flow diagram | Given in figure 1 | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 | Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years |
| | | (b) Indicate number of participants with missing data for each variable of interest | Se figure 1 | Excluded individuals |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow- |

| | | | | |
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| | | | | up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | *6* | There were seven cases of sarcoidosis in total among the cohort.<br>Seropositive RA; 18 cases<br>seronegative RA; 12 cases |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | not applicable | |
| | | (*b*) Report category boundaries when continuous variables were categorized | 5 | Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not possible | |

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| | | | | |
|---|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | none | |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 8 | The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis because the diagnosis is rather unusual. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure but there is also some studies that does not show such a correlation. However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 | Our results reveal a significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust compared to non-exposed and less heavily exposed groups. Silica dust may |

| | | | | |
|---|---|---|---|---|
| | | | | thus be an exogenous factor that initiates sarcoidosis and seropositive RA in genetically predisposed individuals. |
| **Other information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 9 | This study was done with support from Region Örebro County. |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries – a retrospective cohort study



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# Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries – a retrospective cohort study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Region Örebro County for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work
The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Abstract

**Objective**: To study the impact of occupational silica exposure on the incidence rates of sarcoidosis and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries.

**Design**: The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers were compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure, and individual silica exposures were used to compute dose responses.

**Setting**: Personnel records from 10 iron foundries were used to identify workers whose employment began before 2005 which was then linked to the National non-primary outpatient visits register.

**Participants**: The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. The cohort's employment period covers 23 807 person-years at risk.

**Main outcome:** The presented results indicate that moderate to high levels of silica exposure increase risks for sarcoidosis and seropositive rheumatoid arthritis.

**Results**: Mean levels of airborne silica dust in the foundries decreased significantly between the 1970s and 2000s. Incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among highly exposed individuals.

**Conclusions** Our results reveal increased risks for sarcoidosis and seropositive rheumatoid arthritis among individuals with high exposure to silica dust (> 0.048 mg/m$^3$) compared to non-exposed and less exposed groups.


## Strengths and limitations of this study

- This study identifies a possible trigger for sarcoidosis as well as seropositive rheumatoid arthritis.
- This study draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set.
- The diagnoses were based on data recorded in the Swedish national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- The study's main weakness is that despite its relatively large sample size, the dataset only includes a few cases of sarcoidosis as the diagnosis is rather unusual.
- As this study is a register study it provides no indications of other exposures that can trigger rheumatoid arthritis and sarcoidosis.


## Keywords

Sarcoidosis, Rheumatoid arthritis, Silica

## Background

Sarcoidosis is an inflammatory disease that involves the formation of granulomas, mainly in the lungs and/or intrathoracic lymph nodes, but several other organs may also be affected (1). It is diagnosed by biopsy - usually via bronchoscopy if there is lung involvement. Sarcoidosis has no clear etiology, and it is estimated that it has an annual incidence of 11.5 per 100 000 in Sweden (2). Its frequency peaks among individuals aged between 20 and 45 years. Although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals (1, 3). One such suspected environmental factor is silica or silica dust, but only a few studies on silica and sarcoidosis have been published. However, administration of silica via the gastrointestinal tract or intravenously reportedly promotes granuloma development in mice infected with mycobacteria (4). There have also been reports of persistent sarcoidosis going into regression upon cessation of silica exposure (5, 6). Moreover, a cohort study of workers in a limestone (diatomaceous earth) quarry in Iceland found a sarcoidosis incidence rate of 9.3 per 100,000, compared to just 0.5-2.7 per 100 000 for the Icelandic population as a whole (7). While this was taken to suggest that silica exposure may increase the risk for sarcoidosis, the sample was too small to draw firm conclusions (7). A large case-control study from the US suggested that silica is associated with a range of diseases in addition to silicosis, including lung cancer, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, and the autoimmune disease rheumatoid arthritis (RA) (8). While this study found that silica exposure increased risks for various autoimmune diseases (including systemic lupus erythematosus and systemic sclerosis), it did not indicate any connection with sarcoidosis.

Silica exposure is known to cause a fibrotic and potentially fatal lung disease called silicosis (9). Silicosis is currently rare in Sweden because of legislation against silica and silica dust exposure, which has successfully reduced occupational exposure levels (10). This legislation also requires people who are occupationally exposed to silica dust to undergo regular medical checks including physical examinations with spirometry and chest X-rays to ensure the absence of lung disease (11). To study the impact of occupational silica exposure on the risk of sarcoidosis, we used a cohort of silica-exposed workers from Swedish iron foundries (10).

As silica exposure also putatively plays important roles in other inflammatory diseases such as RA (8), we also investigated the risk for RA in the studied cohort. RA and sarcoidosis are both inflammatory diseases, albeit with different symptoms. Thus, the environmental factors that trigger them in genetically predisposed individuals may be similar (1, 12).

Earlier studies have shown that seropositive RA can be initiated within the respiratory system by autoimmune responses to citrullinated peptides (13). A Swedish cohort study found that silica exposure combined with smoking is associated with an increased risk of developing anti-citrullinated protein antibody (ACPA)-positive RA (12).

At our clinic, we have recently had some patients with pulmonary sarcoidosis who also experienced occupational exposure to silica. This prompted us to investigate whether silica dust could cause sarcoidosis, and since these patients now had sarcoidosis, whether it would be advisable for them to stop their occupational exposure to silica.

## Methods and statistical analysis

Data from 10 iron foundries' lists of employees were available in this study (10, 14). The foundries' personnel records were used to identify male workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded, for reasons shown in Figure 1. Thus, the final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. Overall, the cohort's employment period represents 23 807 person-years at risk.

All Swedish residents have a unique personal identification number and equal access to health care and hospital services. This enables retrieval of patient data from various registers, providing unique opportunities to analyze morbidity across the entire patient population. Such nation-wide patient registers are well suited for epidemiological studies.

The cohort was linked to the "National non-primary outpatient care register", which is maintained and validated by the Swedish National Board of Health and Welfare, which contains data on registered outpatients of health care facilities throughout Sweden for all years since 2001. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).The sarcoidosis and RA morbidity analyses covered the period from 2001 (when the National non-primary outpatient care register started) through to 2013. Information on the workers' vital status and emigration status as of the 31$^{st}$ of December 2013 was obtained from the Swedish population registry.

The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis of either sarcoidosis or RA was registered if it occurred before then.

The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) and RA (classified as M05 and M06 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference (derived from the "National non-primary outpatient care register"). Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers.

The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240 to 600 minutes and were corrected to obtain 8-hour time weighted average (8-hour TWA) concentrations, representing exposures over a full workday. A total of 1 667 silica measurements from the 10 foundries were included in the study.

A mixed model was used to calculate silica exposure concentrations for workers in four time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (Swedish equivalents of: caster, core maker, fettler, furnace and ladle repairman, maintenance man, melter, molder, sand mixer, shakeout operative, transportation worker, other specified, many jobs, foundry worker, and

other unspecified) in each of the 10 foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures (mg/m$^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in mg/m$^3$ and categorized into four dose groups (quartiles):<0.023 mg/m$^3$, 0.024-0.035 mg/m$^3$, 0.036-0.047 mg/m$^3$ and >0.048 mg/m$^3$. Because we lack data from before 1968, exposure times before this year were estimated based on the silica level after 1968. The exposures for the groups 'Other specified', 'Foundry workers' and 'Other unspecified' were taken to equal the mean exposure for all the other job classes. The exposure measurement database and exposure modelling are presented elsewhere (15).

## Patient involvement

No patients were involved in the design or conduct of this register study.

The study was approved by the Ethical Committee in Uppsala, Sweden; DNR 2015/066.

## Results

Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years (Table 1). The total range of employment was 1 to 52 years and the mean duration of employment was 11 years. As shown in Table 1, the cohort included workers representing a wide variety of job categories; the most frequent were fettler (20%) and core maker (11.3%). However, many of the workers had been employed in several capacities during the study period (Table 1).

Silica exposure had been measured for workers of all the job categories, and was found to vary between 0.0054-4.9 mg/m$^3$ (Table 2). The highest measurements were well above the Swedish occupational exposure limit (OEL) of 0.1 mg/m$^3$, but both the mean and median measurements for workers of most job categories were below the OEL, except for furnace and ladle repairmen (Table 2). Furnace and ladle repairmen had the highest mean exposure in this study, but fettlers and sand mixers also had exposure values above the cohort mean (Table 2).

Sorting the silica measurements according to their date of acquisition revealed that mean levels of airborne silica dust declined significantly over time, from 0.14 mg/m$^3$ in the 1970s to 0.073 mg/m$^3$ in the 2000s (P <0.0001). Concomitantly, the median exposure to silica dust fell from 0.07 mg/m$^3$ in the 1970s to 0.028 in the 2000s (Table 2).

The mean exposure varied between 0.033 mg/m$^3$ and 0.15 mg/m$^3$ and differed somewhat among the companies that participated in this study (Table 2).

The airborne silica dust measurements presented in Table 2 were used to derive estimated exposures for workers of all job categories in the cohort (as described in Table 1) using a Mixed Model. The resulting estimated doses for each job category are shown in Table 3.

There is some job-dependent variation in estimated doses, but most of this variation relates to employment during the early stages of the measurement period (i.e. before and during the 1970s).

For all cases the concentration of respirable quartz derived from the mixed model based on employment duration, job title, time period, specific foundry and exposure time was expressed as an average annual exposure in mg/m$^3$. There were seven cases of sarcoidosis in total among the cohort. This number was too small to permit analysis of risks' relationships with job categories or companies, but the sarcoidosis was distributed across the foundries. However, four of the sarcoidosis patients were in the highest quartile for silica exposure, suggesting that exposure did increase the incidence of the disease (SIR 3.92; 95 % CI = 1.07-10.03) (Table 4).

We found an increased risk of RA, apparently due to airborne silica exposure, in our cohort (30 cases; SIR 1.52, 95% CI 1.00 - 2.21). When we investigated seropositive RA and seronegative RA separately, we found a statistically significant increase in risk for seropositive RA (18 cases; SIR 1.70, 95 % CI = 1.01-2.69) but not seronegative RA (12 cases; SIR 1.41, 95 % CI = 0.68-2.59).The incidence of seropositive RA was then related to silica exposure by dividing the cohort into quartiles, as previously done for sarcoidosis. Here again we observed increasing incidence with higher exposure. The increased risk of seropositive RA was significant (SIR 2.59, 95 % CI = 1.24-4.76) for the most exposed

group (exposure above 0.048 mg/m$^3$ per year; see Table 5). No such dose-dependent risk was observed for seronegative RA (data not shown).

## Discussion

The results of this work indicate dose-response relationships between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. This is consistent with suggestions in several previous case and population studies of a link between the incidence of sarcoidosis and silica exposure (5-8). Another study found no such correlation (9), but the endpoint in that study was death, which may explain the lack of a detected correlation as since sarcoidosis rarely causes death.It has been suggested that sarcoidosis might be caused by exposure to an exogenous factor in individuals who are genetically susceptible (1, 3). Our study suggests that silica may be one such factor. Because the cases of sarcoidosis identified in this work were distributed across the foundries, rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster.

Several studies have linked RA with silica exposure (9, 12, 13), putatively because some factor associated with silica exposure (and smoking) may induce an immunological response to citrullinated antigens, leading to the onset of seropositive RA (ACPA-positive RA). We also found that workers with the highest levels of silica exposure had the highest risk for seropositive RA. We lack complete information on the workers' smoking habits, but as the prevalence of smoking has decreased over time, as well as silica exposure, the proportion of smokers (or ex-smokers) may be highest in the highly exposed group, which could affect the prevalence of RA.

A potential causative mechanism of both seropositive RA and sarcoidosis is activation of an immune response in genetically predisposed individuals by an inhaled exogenous substance. As noted above, our results suggest that inhaled silica dust may be such a causative exogenous factor.

A strength of the study is that it draws on exposure measurements acquired at workspaces since 1968, which constitute a uniquely long-running data set. Moreover, the diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires. Finally, the results were compared to data for the general Swedish population in the corresponding years, which allowed us to account for annual variation.

The study's main weakness is that despite its relatively large sample size, the data set includes only a few cases of sarcoidosis. We assume that the reference group was unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study it provides no indications of other exposures that can trigger RA and sarcoidosis.

It is possible that some of the sarcoidosis cases considered in this work are asymptomatic patients whose condition was only detected because silica-exposed workers are required to undergo mandatory health checks, including chest X-rays, which could result in overestimation of the risk for sarcoidosis. However, because workers are required to have a health check (including an X-ray examination) before starting work in a job involving exposure to silica dust, we believe that such asymptomatic cases would probably be detected before the individual in question started working. We therefore assume that all the sarcoidosis cases identified in this study developed after the individuals in question began working at the foundries.

The increased risk for sarcoidosis cannot be explained by the X-rays that employees in the studied occupations undergo. We saw no increased incidence of sarcoidosis among the low exposure groups, who were required to have the same number of chest X-rays as the high exposure workers, thus chest x-rays cannot explain the silica dust dose-related differences in incidence between the high and low exposure groups.. Additionally, the sarcoidosis sufferers had been working at the foundries for the same length of time as the rest of the cohort (the mean working time for both groups was 11 years) so they would have been subjected to the same number of X-ray examinations.

## Conclusions

Our results reveal increased risks for sarcoidosis (SIR 3.94, 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (SIR 2.59, 95% CI 1.24-4.76) among individuals with high exposure to silica dust (> 0.048 mg/m$^3$) compared to non-exposed and less heavily exposed groups.

## Contributorship

PV, ILB and PG conceived and designed the study. LA was responsible for the data collection, and ILB for the main data analysis. PV, ILB and PG interpreted the results. PV, ILB and PG wrote the manuscript with input from LA. All authors approved the final version.

## Competing interests

The authors have no competing interests in connection with this paper

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## Data sharing statement

No additional data are available.

## References


1. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet. 2014;383(9923):1155-67.
2. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016.
3. SwedishRespiratorySociety. National Guidelines for Treatment of Sarcoidosis. 2014.
4. Yeager H, Gopalan S, Mathew P, Lawless O, Bellanti JA. Sarcoidosis: can a murine model help define a role for silica? Med Hypotheses. 2012;78(1):36-8.
5. Sola R, Boj M, Hernandez-Flix S, Camprubi M. Silica in oral drugs as a possible sarcoidosis-inducing antigen. Lancet. 2009;373(9679):1943-4.
6. Drent M, Wijnen PA, Boots AW, Bast A. Cat litter is a possible trigger for sarcoidosis. Eur Respir J. 2012;39(1):221-2.
7. Rafnsson V, Ingimarsson O, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. Occup Environ Med. 1998;55(10):657-60.
8. Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med. 2003;60(2):122-9.
9. Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012;379(9830):2008-18.
10. Andersson L, Bryngelsson IL, Ohlson CG, Naystrom P, Lilja BG, Westberg H. Quartz and dust exposure in Swedish iron foundries. J Occup Environ Hyg. 2009;6(1):9-18.
11. SwedishWorkEnvironmentAuthority. Medical Assessment in the Workplace. 2005.
12. Stolt P, Yahya A, Bengtsson C, Kallberg H, Ronnelid J, Lundberg I, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. Ann Rheum Dis. 2010;69(6):1072-6.
13. Perry E, Kelly C, Eggleton P, De Soyza A, Hutchinson D. The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? Rheumatology (Oxford). 2014;53(11):1940-50.
14. Westberg H, Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG. Cancer morbidity and quartz exposure in Swedish iron foundries. Int Arch Occup Environ Health. 2013;86(5):499-507.
15. Andersson L, Bryngelsson IL, Ngo Y, Ohlson CG, Westberg H. Exposure assessment and modeling of quartz in Swedish iron foundries for a nested case-control study on lung cancer. J Occup Environ Hyg. 2012;9(2):110-9.

Table 1: General information about the cohort

| | | Number of subjects | Percent |
|---|---|---|---|
| Start of work (year) | 1930-1949 | 55 | 2.5 |
| | 1950-1969 | 425 | 19.4 |
| | 1970 – 1989 | 1 035 | 47.3 |
| | 1990+ | 672 | 30.7 |
| Years of employment | 1-<2 | 357 | 16.3 |
| | 2-10 | 936 | 42.8 |
| | 11-20 | 472 | 21.5 |
| | 20+ | 422 | 19.3 |
| Job categories | many jobs | 249 | 11.4 |
| | caster | 64 | 2.9 |
| | molder | 209 | 9.6 |
| | core maker | 246 | 11.3 |
| | sand mixer | 7 | 0.3 |
| | melter | 131 | 6.0 |
| | furnace and ladle repairman | 6 | 0.3 |
| | shakeout operative | 18 | 1.0 |
| | fettler | 430 | 20.0 |
| | Maintenance man | 171 | 7.8 |
| | Transportation worker | 26 | 1.2 |
| | other specified | 96 | 4.4 |
| | foundry worker | 196 | 9.0 |
| | office work | 48 | 2.2 |
| | other unspecified | 290 | 13.2 |

Table 2: Measurements of silica exposure for workers of indicated job categories (mg/m$^3$)

| Job title | N | Mean | Median | Minimum | Maximum | Std. Deviation |
|---|---|---|---|---|---|---|
| caster | 68 | 0.033 | 0.018 | 0.0054 | 0.17 | 0.038 |
| molder | 257 | 0.058 | 0.039 | 0.0034 | 0.98 | 0.081 |
| core maker | 171 | 0.024 | 0.017 | 0.003 | 0.19 | 0.023 |
| fettler | 573 | 0.087 | 0.039 | 0.0025 | 2.1 | 0.16 |
| sand mixer | 91 | 0.088 | 0.034 | 0.0036 | 1.1 | 0.18 |
| furnace and ladle repairman | 71 | 0.42 | 0.12 | 0.0028 | 4.9 | 0.76 |
| melter | 111 | 0.052 | 0.022 | 0.0038 | 0.52 | 0.079 |
| Transportation worker | 29 | 0.031 | 0.023 | 0.0018 | 0.11 | 0.022 |
| Maintenance man | 67 | 0.054 | 0.029 | 0.0052 | 0.67 | 0.09 |
| shakeout operative | 148 | 0.079 | 0.037 | 0.0047 | 3.3 | 0.29 |
| other | 81 | 0.088 | 0.03 | 0.005 | 2.1 | 0.25 |
| | | | | | | |
| Years for measurement | | | | | | |
| 1970-1979 | 303 | 0.14 | 0.07 | 0.003 | 3.3 | 0.26 |
| 1980-1989 | 347 | 0.08 | 0.027 | 0.0036 | 4.9 | 0.31 |
| 1990-1999 | 472 | 0.062 | 0.026 | 0.0018 | 1.9 | 0.16 |
| 2000-2006 | 545 | 0.073 | 0.028 | 0.0033 | 2.1 | 0.2 |
| | | | | | | |
| Company | | | | | | |
| 1 | 135 | 0.065 | 0.044 | 0.0035 | 0.29 | 0.062 |
| 2 | 53 | 0.075 | 0.035 | 0.0054 | 0.89 | 0.14 |
| 3 | 213 | 0.088 | 0.05 | 0.0083 | 0.98 | 0.13 |
| 4 | 250 | 0.15 | 0.047 | 0.0038 | 4.9 | 0.43 |
| 6 | 58 | 0.099 | 0.024 | 0.0038 | 1.4 | 0.21 |
| 7 | 320 | 0.079 | 0.036 | 0.0018 | 2.1 | 0.21 |
| 8 | 306 | 0.063 | 0.018 | 0.0036 | 3.3 | 0.23 |
| 9 | 35 | 0.092 | 0.056 | 0.0084 | 0.28 | 0.083 |
| 10 | 174 | 0.033 | 0.027 | 0.0037 | 0.3 | 0.032 |
| 11 | 123 | 0.076 | 0.031 | 0.0033 | 0.77 | 0.12 |
| Total | 1667 | 0.083 | 0.033 | 0.0018 | 4.9 | 0.23 |

Table 3: Estimated silica dose per year (mg/m$^3$) for workers of indicated job categories based on a mixed model.

| Job title | N | Mean | Median | Min | Max | Std. Deviation |
|---|---|---|---|---|---|---|
| many jobs | 249 | 0.04 | 0.039 | 0.017 | 0.12 | 0.013 |
| caster | 64 | 0.028 | 0.023 | 0.015 | 0.06 | 0.012 |
| molder | 209 | 0.042 | 0.032 | 0.018 | 0.098 | 0.023 |
| core maker | 246 | 0.023 | 0.02 | 0.012 | 0.061 | 0.0096 |
| sand mixer | 7 | 0.068 | 0.063 | 0.052 | 0.089 | 0.016 |
| melter | 131 | 0.03 | 0.026 | 0.016 | 0.085 | 0.015 |
| furnace and ladle repairman | 6 | 0.15 | 0.14 | 0.11 | 0.21 | 0.033 |
| shakeout operative | 18 | 0.056 | 0.054 | 0.026 | 0.1 | 0.022 |
| fettler | 430 | 0.044 | 0.037 | 0.023 | 0.12 | 0.016 |
| Maintenance man | 171 | 0.041 | 0.036 | 0.021 | 0.077 | 0.016 |
| Transportation worker | 26 | 0.038 | 0.044 | 0.019 | 0.059 | 0.012 |
| other specified | 96 | 0.04 | 0.036 | 0.021 | 0.089 | 0.016 |
| foundry worker | 196 | 0.056 | 0.06 | 0.024 | 0.1 | 0.017 |
| office work | 48 | 0.037 | 0.033 | 0.021 | 0.073 | 0.011 |
| other unspecified | 290 | 0.038 | 0.028 | 0.02 | 0.11 | 0.021 |

Table 4: Incidence of sarcoidosis in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | Person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| Total | 2 187 | 23 748 | 7 | 4.98 | 1.41 | 0.56-2.89 |
| 0.012 - 0.023 | 546 | 6 279 | 0 | 1.38 | - | - |
| 0.024 - 0.035 | 547 | 6 141 | 1 | 1.35 | 0.74 | 0.02-4.12 |
| 0.036 - 0.047 | 547 | 5 889 | 2 | 1.24 | 1.62 | 0.20-5.84 |
| 0.048+ | 547 | 5 439 | 4 | 1.02 | 3.942 | 1.07-10.08 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles.

Table 5: Incidence of seropositive rheumatoid arthritis (RA) in the cohort, grouped by yearly average exposure to airborne silica dust

| Mean silica ($mg/m^3$) per year* | N | Person-years | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|---|---|
| | 2 187 | 23 689 | 18 | 10.6 | 1.70 | 1.01-2.69 |
| 0.012 - 0.023 | 546 | 6 267 | 2 | 1.667 | 1.20 | 0.15-4.32 |
| 0.024 - 0.035 | 547 | 6 144 | 1 | 2.35 | 0.43 | 0.01-2.37 |
| 0.036 - 0.047 | 547 | 5 868 | 5 | 2.70 | 1.86 | 0.60-4.33 |
| 0.048+ | 547 | 5 410 | 10 | 3.90 | 2.59 | 1.24-4.76 |

* Average annual silica exposure ($mg/m^3$), divided into quartiles

## Figure Legend

Figure 1: Selection of participants for inclusion in the cohort

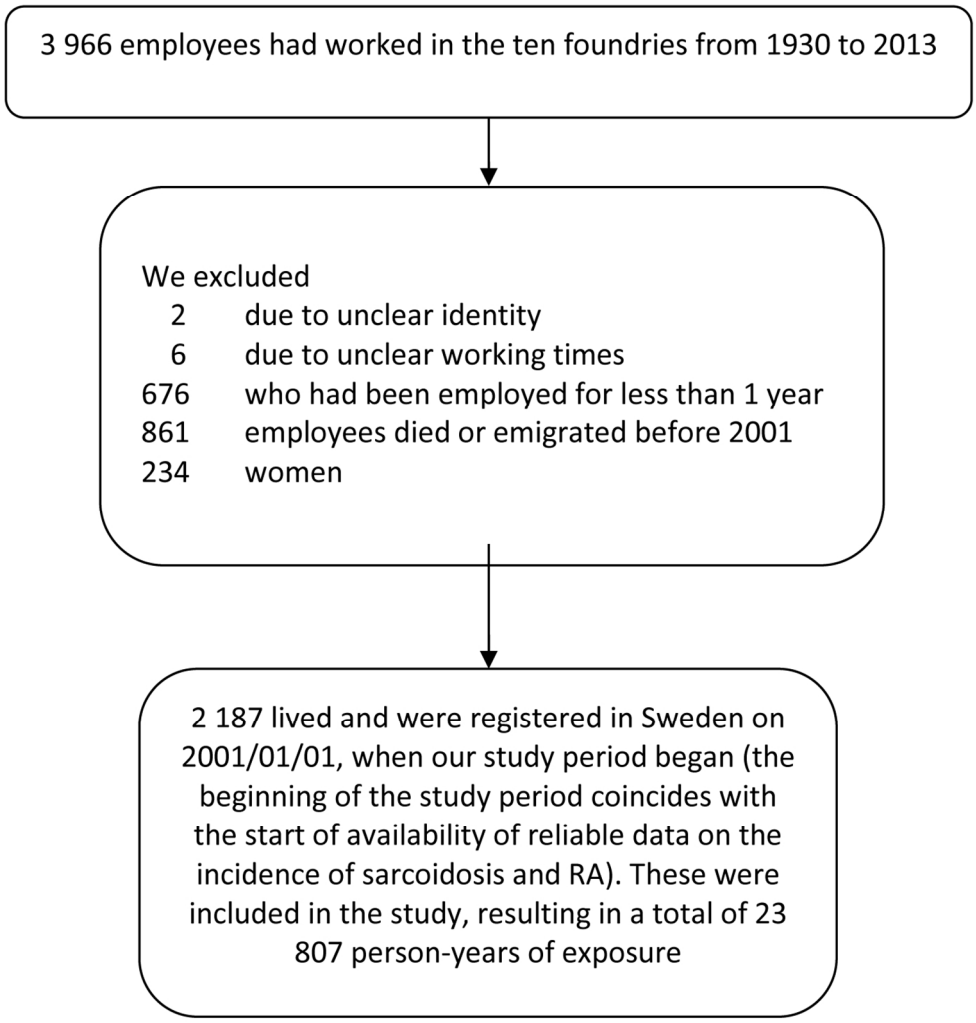


Figure 1: Selection of participants for inclusion in the cohort

121x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 | Register study |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 | The prevalence of sarcoidosis and rheumatoid arthritis in a cohort of silica exposed workers where compared to the prevalence in the general Swedish population in this register study. A mixed model was used to calculate silica exposure and individual silica exposures were used to compute dose responses. Mean levels of airborne silica dust decreased significantly between the 1970s and the 2000s. The incidence rates of sarcoidosis (3.94; 95% CI 1.07-10.08) and seropositive rheumatoid arthritis (2.59; 95% CI 1.24-4.76) were significantly higher among high exposed individuals. |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 | Sarcoidosis has no clear etiology, although its etiology is unknown, it is believed to be multi-factorial and potentially triggered by environmental factors in genetically predisposed individuals. One such suspected environmental factor is silica or silica dust |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 and 3 | To study the impact of occupational silica exposure on the incidence rate of sarcoidosis |

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| | | | | and rheumatoid arthritis in a cohort of exposed workers in Swedish iron foundries. |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 | Data from ten iron foundries' lists of employees were available in this study. The cohort was linked to the "National non-primary outpatient care register", which is maintained by the Swedish National Board of Health and Welfare and contains data for all years since 2001. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow-up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 and figure 1 | The foundries' personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded. The final cohort consisted of 2 187 silica-exposed male workers who had been employed for at least one year and were still alive without having emigrated when the follow-up study began. As a whole, the cohort's employment |

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| | | | | period represents 23 807 person-years at risk. |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 2, 3, 4 and 8 | Sarkodosis and RA. Sarcoidosis was defined according to the International Classification 10 (ICD 10) D86 (0, 1, 2, 3, 8) and RA M05 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9) and M06 (0, 1, 2, 3, 4, 8, 9).<br>Silica exposure. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *4* | The silica exposure data used in this study were personal sampling measurements of respirable silica acquired between 1968 and 2006. The measurement times range from 240-600 minutes and were corrected to obtain 8-hour time weighted average concentrations (8-hour TWA), representing a full workday. A total of 1 667 silica measurements from the ten foundries were included in the study.<br>For sarcoidosis and RA The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers |

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| | | | | of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed numbers. |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8 | As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. Because the cases of sarcoidosis identified in this work were distributed across the foundries rather than forming clusters associated with individual plants, we exclude the possibility that the observed incidence rates could be due to a local cluster. |
| Study size | 10 | Explain how the study size was arrived at | 4 and figure 1 | The foundries' (where we had silica measurements) personnel records were used to identify workers whose employment began before 2005, yielding an initial cohort of 3 966 subjects, of whom 1 779 were excluded: 2 due to unclear identity, 6 due to unclear working times, 676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |

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| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4 and 5 | A mixed model was used to calculate silica exposure concentrations for workers in four different time periods (1968-1979, 1980 -1989, 1990-1999 and 2000-2006) with different job titles (caster, core maker, fettler, furnace and ladle repair, maintenance, melter, moulder, sand mixer, shake out, transportation, other specified, many jobs, foundry workers, and other unspecified) in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. Individual silica exposures ($mg/m^3$) were used to calculate dose responses. Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 4 | A mixed model was used to calculate silica exposure concentrations<br>The person-years at risk were calculated and stratified according to gender, 5-year age groups, and 1-year calendar periods. The expected numbers of people with sarcoidosis (classified as D86 under the ICD10 standards) for these strata were calculated using data for the general Swedish population as a reference. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution of the observed |

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| | | | | numbers. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | not applicable | |
| | | (*c*) Explain how missing data were addressed | See figure 1 | Excluded individuals |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | not applicable | |
| | | (*e*) Describe any sensitivity analyses | Not done in this study | |
| **Results** | | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 | The initial cohort had 3 966 subjects, of whom 1 779 were excluded: |
| | | (b) Give reasons for non-participation at each stage | Figure 1 | 2 due to unclear identity, 6 due to unclear working times,<br>676 who had been employed for less than 1 year, 861 employees died or emigrated before 2001 and 234 women. |
| | | (c) Consider use of a flow diagram | Given in figure 1 | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 | Most of the 2187 workers in the cohort began working at the foundries in the 1970s or 1980s, but some had started as early as during the 1930s (Table 1). All of the study participants were male. Almost half had been employed in the foundries for 2-10 years, but nearly 40% had worked in foundries for over 10 years |
| | | (b) Indicate number of participants with missing data for each variable of interest | Se figure 1 | Excluded individuals |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 4 | The follow-up period for each worker in the cohort began in 2001 or at the start of the worker's employment in the foundry, whichever came first. The follow- |

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| | | | | up period ended at the end of 2013 or on the date of the worker's, death or emigration or on the date a diagnosis for sarcoidosis either RA was registered if they occurred before then. |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | *6* | There were seven cases of sarcoidosis in total among the cohort.<br>Seropositive RA; 18 cases<br>seronegative RA; 12 cases |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | not applicable | |
| | | (*b*) Report category boundaries when continuous variables were categorized | 5 | Exposure to respirable silica was thus defined as the average exposure per year in $mg/m^3$ and categorized into four dose groups (quartiles):<0.023 $mg/m^3$, 0.024-0.035 $mg/m^3$, 0.036-0.047 $mg/m^3$ and >0.048 $mg/m^3$. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not possible | |

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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | none | |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 8 | The study's main weakness is that despite its relatively large sample size, the dataset includes only a few cases of sarcoidosis because the diagnosis is rather unusual. We assume that the reference group is unexposed, but there were probably some silica-exposed individuals in this group too. As this study is a register study we have no knowledge of other exposure that can trigger RA and Sarcoidosis. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8 | The results of this work indicate a dose-response relationship between silica exposure and incidence of both sarcoidosis and RA in Swedish foundry workers. Some previous case and population studies have suggested a link between the incidence of sarcoidosis and silica exposure but there is also some studies that does not show such a correlation. However, the endpoint in that study was death, which may have caused a correlation to be missed since sarcoidosis rarely causes death |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 | Our results reveal a significant increase in the incidence rate of sarcoidosis and seropositive RA among individuals with high exposure to silica dust compared to non-exposed and less heavily exposed groups. Silica dust may |

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| | | | | thus be an exogenous factor that initiates sarcoidosis and seropositive RA in genetically predisposed individuals. |
| **Other information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 9 | This study was done with support from Region Örebro County. |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.